ANNALS OF THE RHEUMATIC DISEASES

EDITOR
W. S. C. COPEMAN

ASSISTANT EDITOR
OSWALD SAVAGE

EDITORIAL COMMITTEE
E. G. L. BYWATERS
D. H. COLLINS
J. H. KELLGREN
H. OSMOND-CLARKE

EDITORIAL BOARD
G. R. CAMERON
NORMAN CAPENER
PHILIP S. HENCH (U.S.A.)
SIR STANLEY DAVIDSON
J. J. R. DUTHIE
G. D. KERSLEY
EDWARD W. BOLAND (U.S.A.)
E. LEWIS-FANING
R. E. TUNBRIDGE
WALTER BAUER (U.S.A.)

PRESIDENT OF THE AMERICAN RHEUMATISM ASSOCIATION
PRESIDENT OF THE CANADIAN RHEUMATISM ASSOCIATION
PRESIDENT OF THE EUROPEAN LEAGUE AGAINST RHEUMATISM
PRESIDENT OF THE INTERNATIONAL LEAGUE AGAINST RHEUMATISM
and the EDITOR of the *British Medical Journal*

APPOINTED BY THE
BRITISH MEDICAL ASSOCIATION AND THE EMPIRE RHEUMATISM COUNCIL

VOLUME XV, 1956

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD
109 KINGSWAY LONDON WC2 AND ASHFORD KENT

CONTENTS OF VOLUME XV

No. 1. *MARCH, 1956*

	PAGE
Rheumatoid Arthritis in a Population Sample. J. H. KELLGREN and J. S. LAWRENCE	1
Nature of Anaemia in Rheumatoid Arthritis. II. Survival of Transfused Erythrocytes in Patients with Rheumatoid Arthritis. W. R. M. ALEXANDER, J. RICHMOND, L. M. H. ROY, and J. J. R. DUTHIE	12
Kerato-Conjunctivitis Sicca and Rheumatoid Arthritis. MALCOLM THOMPSON and STELLA EADIE	21
Pulmonary Changes in Disseminated Lupus Erythematosus. J. D. AITCHISON and A. WYNN WILLIAMS	26
Modern Trends in Acute Rheumatism. S. LEFF	33
Spondylitis in Post-Pubertal Patients with Rheumatoid Arthritis of Juvenile Onset. MORRIS ZIFF, VINCENT CONTRERAS, and CURRIER MCEWEN	40
Hypertrophic Osteo-Arthropathy in Polyarteritis. R. R. H. LOVELL and G. B. D. SCOTT ..	46
Clinical Trial of Intravenous and Intramuscular Iron in Rheumatoid Arthritis. J. B. MILLARD and H. STUART BARBER..	51
Radiological Signs of Rheumatoid Arthritis. J. H. KELLGREN and FRIDA BIER	55
American Rheumatism Association. Proceedings of Second Interim Scientific Session, 1955 ..	61
Book Reviews	80
Heberden Society	81
Società Italiana di Reumatologia. Third Acqui Prize, 1957	82
Ligue Internationale contre le Rhumatisme. IX International Congress, 1957	83
II International Congress on Physiotherapy, 1956	83
Empire Rheumatism Council	83
Abstracts	84

No. 2. *JUNE, 1956*

Measurement of Bone Density. DONALD MAINLAND	115
Ankylosing Spondylitis. D. O'CONNELL	119
Acquired Resistance to Corticotropins. H. F. WEST	124
Pilot Study of Intra-Articular Procaine and Hydrocortisone Acetate in Rheumatoid Arthritis. G. R. FEARNLEY, RITA LACKNER, R. I. MEANOCK, and E. G. L. BYWATERS	134
Uveitis and Rheumatic Diseases. A. STANWORTH and J. SHARP	140
Haemodilution in Rheumatoid Disease. M. R. JEFFREY	151
Decline of Acute Rheumatism. R. A. N. HITCHENS	160
Comparison of Cortisone Acetate and a Codeine Mixture as Adjuvant Treatment in Judet Arthroplasty. G. P. ARDEN	173
Pericarditis complicating Rheumatoid Arthritis. A. E. THOMAS and W. K. C. MORGAN ..	176
Book Reviews	180
First International Symposium on Rheumatic Fever	181
Società Italiana di Reumatologia	182
Empire Rheumatism Council: Nineteenth Annual Report, 1955	183
Sociedad Española de Reumatismo	188
Heberden Society: Annual Report, 1955	189
Australian Rheumatism Council: Report for 1954-1955	191
Abstracts	193

108612

No. 3. *SEPTEMBER, 1956*

PAGE

Rheumatoid Arthritis and the Positive L.E.-Cell Phenomenon. J. H. KIEVITS, J. GOSLINGS, H. R. E. SCHUIT, and W. HIJMANS .. 211

Nature of Anaemia in Rheumatoid Arthritis. III. J. RICHMOND, D. L. GARDNER, L. M. H. ROY, and J. J. R. DUTHIE .. 217

Use of the Hypospray Jet Injector for the Intra-Articular and Local Administration of Hydrocortisone Acetate. MORRIS ZIFF, VINCENT CONTRERAS, and FRANK R. SCHMID .. 227

Therapeutic Trials in Acute Gouty Arthritis. MELVIN H. LEVIN, STANLEY MARCUS, DAVID STRANGE, and ROBERT L. SWEZEY .. 233

Clinical and Metabolic Effects of $\triangle^1$-Dehydro-9-Alpha-Fluoro Hydrocortisone Acetate. L. VILLA, G. SALA, and C. B. BALLABIO .. 237

Changes in the Intra-Articular Temperature of the Knee with Cutaneous Vasoconstriction and Vasodilatation of the Toes in Normal Subjects. RAYMOND PENNEYS and NATHAN M. SMUKLER 241

Modified Waaler-Rose Reaction employing Sensitized Human Cells. H. J. GIBSON and N. R. LING 246

Chloroquine and Rheumatoid Arthritis. A. FREEDMAN .. 251

Hydrocortisone *Tertiary*-Butylacetate for Intra-Articular Therapy in Rheumatic Diseases. JACK ZUCKNER, OTAKAR MACHEK, and ARCH M. AHERN .. 258

Book Reviews .. 261

Heberden Society .. 263

American Rheumatism Association .. 266

Ligue Internationale contre le Rhumatisme .. 267

Canadian Rheumatism Association .. 267

Abstracts .. 273

No. 4. *DECEMBER, 1956*

Growth in Still's Disease. B. M. ANSELL and E. G. L. BYWATERS .. 295

Studies in Osteo-Arthritis using Intra-Articular Temperature Response to Injection of Hydrocortisone Acetate and Prednisone. JOSEPH L. HOLLANDER and ROBERT MOORE .. 320

Absorption of Hydrocortisone from the Joint Cavity into the Circulation. MARTTI OKA .. 327

Local Injection of Hydrocortisone and Procaine in Osteo-Arthritis of the Hip Joint. V. M. LEVEAUX and C. E. QUIN .. 330

Laboratory Aids in Steroid Therapy. J. H. GLYN .. 338

A Hand Corset. H. HERSCHEL .. 346

Psoriasis and Arthritis. V. WRIGHT .. 348

Studies of Hyaluronic Acid in Rheumatoid Arthritis. N. EGELIUS, E. JONSSON, and L. SUNDBLAD 357

Response by Antibodies to Tissue Antigens in the Course of Rheumatic Fever. V. WAGNER and V. REJHOLEC .. 364

Book Reviews .. 373

Obituary: Mathieu-Pierre Weil .. 373

American Rheumatism Association: Proceedings of Annual Meeting, 1956 .. 374

Heberden Society .. 410

Arthritis and Rheumatism Foundation .. 412

Abstracts .. 413

Index for 1956 .. 429

Ann. rheum. Dis. (1956), **15**, 1.

RHEUMATOID ARTHRITIS IN A POPULATION SAMPLE

BY

J. H. KELLGREN AND J. S. LAWRENCE*

From the Rheumatism Research Centre, University of Manchester

(RECEIVED FOR PUBLICATION JANUARY 2, 1956)

Many estimates have been made of the prevalence of rheumatic complaints in various populations. In earlier studies information was collected from general practitioners (Ministry of Health, 1924), and later from insurance certificates (Medical Advisory Committee, Scotland, 1945). Field surveys have also been conducted by house-to-house interviews with questionnaires (Woolsey, 1952; Stocks, 1949; Brooke, 1953) and with questionnaires supplemented by clinical examination of individuals with complaints (Edström, 1944; Kellgren, Lawrence, and Aitken-Swan, 1953; Blécourt, 1953).

All these studies have shown that rheumatic complaints as a whole are common, particularly in the older age groups, and that they cause much disability. The prevalence rates for rheumatic complaints as a whole in these different studies are similar if one takes into account the different methods employed for collecting data; but attempts to classify rheumatic complaints into diagnostic categories have given widely divergent results. Thus estimates of the prevalence of rheumatoid arthritis have ranged from 0·4 to 2·3 per cent., and of osteo-arthritis from 0·04 to 6·2 per cent., the lowest rates being those for self-diagnosis in reply to questionnaires published by Stocks (1949), and the highest those for clinical examination in the field obtained by Kellgren and others (1953).

Owing to the lack of diagnostic definition and objective criteria of disease, these divergent estimates of prevalence probably reflect differences of method and language amongst observers rather than a differing incidence of disease, and if any useful epidemiological studies are to be carried out in this field of medicine more precise and reproducible diagnostic definitions must be used and more precise objective criteria of disease must be introduced. The diagnostic difficulty is great, since conditions such as rheumatoid arthritis and osteo-arthritis can only be recognized clinically with certainty in their most typical and severe forms, which are rare, whereas lesser degrees of arthritis are common and these merge imperceptibly with rheumatic complaints of undetermined nature. Furthermore, the association between pain and anatomical changes in the joints is incomplete, so that complaint rates alone cannot safely be accepted as indices of pathological change.

In studies of osteo-arthritis and disk degeneration, some of these difficulties have been overcome by the use of *x* rays of the relevant joints (Kellgren and Lawrence, 1952; Lawrence, 1955). In the diagnosis of rheumatoid arthritis, Miall and his associates have introduced *x* rays of the hands and feet and/or a positive differential sheep cell agglutination test (Rose, Ragan, Pearce, and Lipman, 1948; Ball, 1950) as essential confirmatory criteria (Miall, Caplan, Cochrane, Kilpatrick, and Oldham, 1953; Miall, 1955). These are real advances, but too little is known about the prevalence of *x*-ray changes and positive agglutination tests in the general population.

To elucidate some of these problems we have studied a sample of the general population in great detail, using radiological and serological as well as clinical techniques, and recording all forms of rheumatic disease in defined grades of severity.

Population Studied

In 1949-50 rheumatic complaints were studied amongst the adult inhabitants of a 1 in 10 sample of houses in Leigh, an industrial town in Lancashire with a population of some 48,000. For the present investigation all individuals included in this sample who were in the age group 50-59 years in 1949-50 were selected for study. The second survey was carried out in the autumn of 1954, when the individuals studied were 5 years older and with few exceptions came within the age group 55-64 years.

* In receipt of a grant-in-aid from the Medical Research Council.

Methods of Survey

A preliminary house visit was made by one of us (mostly J.S.L.) who collected information about past and present rheumatic complaints and any resulting disability. A special question was asked about morning stiffness, since Cobb, Warren, Thompson, and Ciocco (1954) and Cobb, Merchant, and Warren (1955) have suggested that morning stiffness might be used as a screening test for rheumatoid arthritis. Such information as could be obtained from clinical examination of the hands was also recorded. An appointment was then made to attend a special examination centre where a more detailed clinical and occupational history was taken.

At this examination the question about morning stiffness was repeated; and a separate question was asked about back pain, lumbago, sciatica, and neuritis. A special question about the occurrence of rheumatism, rheumatic fever, or arthritis in childhood or early adult life was also included, and the replies recorded as "past polyarthritis" with dates and duration as far as these could be ascertained.

The hands were then examined for Heberden's nodes, arthritis of first carpo-metacarpal joint, reduced peripheral circulation, sweating, tendon nodules, and tendon sheath swellings, and each characteristic was recorded as absent or present in doubtful, slight, or severe degree.

A more complete examination of the joints was carried out on a couch, the following characteristics being noted:

(1) pain on movement and pressure,

(2) joint warmth, swelling, effusion, or bony enlargement,

(3) range of motion, whether normal, or slightly or severely restricted, and whether accompanied by crepitus.

The spine was examined standing and a note was made of the spinal curves and mobility. Spinal movements were recorded separately for the cervical and lumbo-dorsal regions.

The findings in the following joints were recorded separately for the left and right sides of the body: proximal interphalangeal and metacarpo-phalangeal joints in the hands, the wrists, elbows, shoulders, hips, knees, ankles, tarsal joints, and the lateral and first metatarso-phalangeal joints in the feet. The presence of subcutaneous nodules was also recorded. An opinion had to be expressed about the presence of rheumatoid arthritis, generalized osteo-arthritis as defined by Kellgren and Moore (1952), local traumatic or secondary osteo-arthritis, disk degeneration or prolapse, other defined rheumatic complaints such as gout, spondylitis, and rheumatic fever, psychogenic rheumatism, and pain of undetermined nature. These diagnostic categories were recorded either as absent or as present in doubtful, slight, moderate, or severe degree. The examiner's impression of the individual's personality, whether normal, neurotic or psychotic, was also recorded.

The height and weight were recorded, and a sample of blood taken for the differential sheep cell agglutination test (D.A.T.). Antero-posterior radiographs were taken of hands, feet, knees, and pelvis, and lateral radiographs of the lumbar and cervical spine. A few individuals who were unable or unwilling to come to the centre were examined and *x*-rayed in their own homes, but in these cases only radiographs of the hands and feet were obtainable.

The information collected was thus fairly extensive and can be analysed from many points of view, but in this report we shall confine ourselves to a study of rheumatoid arthritis.

Completeness of Survey

The records of the previous survey in Leigh, Lancs. (which at that time was a complete 1 in 10 sample) provided 537 persons in the age group selected for study and of these 237 were men. From the home visits it was ascertained that 34 of these individuals had died and 22 had removed from the area, leaving an available total of 481. Of these fourteen refused to be seen, so that the home interview in this study is 97 per cent. complete. 87 refused to be *x*-rayed. In a further thirty cases the blood test was refused or its results were unsatisfactory, so that the serological survey is only 73 per cent. complete (Table I).

Since this is primarily a correlation study, this lapse rate was accepted because of the very considerable labour required for greater completion.

The 1949-50 records and inquiries from relatives showed that amongst the 56 individuals who had died or removed there was no undue prevalance of polyarthritis. The 87 individuals who refused *x* ray were generally without significant rheumatic symptoms except for one woman who at the home interview was judged to have rheumatoid arthritis of moderate severity.

For simplicity, only the results from the 380 persons *x*-rayed will be analysed in detail.

TABLE I

COMPLETENESS OF SURVEY

Sex	No. in 1949-50 Sample	Not Available		Total Available	Refused Interview or Never at Home	Interviewed but Refused *x* Ray	Interview and *x* Ray	Interview, *x* Ray, and Blood Test
		Dead	Moved out of District					
Men	237	25	8	204	6	25	173	163
Women	300	9	14	277	8	62	207	187
Total	537	34	22	481	14	87	380	350

Results

Clinical Findings.—The prevalence of clinical polyarthritis amongst the 380 persons *x*-rayed is shown in Table II. All definite cases, whether slight or severe, are included. In some instances, particularly those with osteo-arthritis, there was no complaint of pain in spite of very definite physical findings in the joints and these cases have been included as positive. Concurrent rheumatoid arthritis and generalized osteo-arthritis were only noted in eight women, although in hospital clinics this combination is fairly frequently seen, but this may simply be due to the fact that only a highly selected sample of the population attends hospital.

TABLE II

CLASSIFICATION OF CLINICAL POLYARTHRITIS

Clinical Diagnosis	Sex			
	Men		Women	
	No.	%	No.	%
Rheumatoid Arthritis only ..	5	3	22	11
Generalized Osteo-arthritis only ..	21	12	69	33
Rheumatoid Arthritis + Generalized Osteo-arthritis ..	0	0	8	4
Psoriatic Arthropathy	1	0·6	0	0
Gout	2	1	0	0
Spondylitis	2	1	0	0
Total Polyarthritis	31	18	99	48
Total Surveyed	173	100	207	100

The clinical findings are similar to those previously reported for the inhabitants of Leigh (Kellgren, Lawrence, and Aitken-Swan, 1953). The usual sex difference is observed—all forms of polyarthritis except gout and spondylitis being more frequent in women.

When we consider the serological and radiological evidence of rheumatoid arthritis some unexpected findings emerge.

Serological Findings.—The D.A.T. was performed by Dr. J. Ball, using his 1950 method, the test being recorded as positive if agglutination occurred in a dilution of 1 : 32 at 18 hrs.

The serological findings in the 163 men and 187 women tested are illustrated in Fig. 1. It is apparent that the general distribution of titres in the two sexes is almost identical. Amongst the men there were eight (5 per cent.) with positive tests, and amongst the women eleven (6 per cent.). If it is assumed that all those not tested would be negative, the minimal prevalence of positive tests in this age group in Leigh would be about 4 per cent., but this is almost certainly not a safe assumption so that the true prevalence is likely to be nearer 5 per cent.

Radiological Findings.—Radiological evidence of rheumatoid arthritis is usually sought in films of the hands and feet, and observer differences of interpretation and the reproducibility of individual readings have been studied recently (Kellgren, 1956). To reduce errors to a minimum the films of the hands and feet in this survey were all taken by a standard technique, and a control bone was included in the hand films. These films were then read three times. The first reading was done jointly by both of us and the second by one of us reading alone. For these two readings rheumatoid changes as a whole were graded as follows:

0 = None,
1 = Doubtful,
2 = Slight,
3 = Moderate,
4 = Severe.

In the third reading, done jointly, porosis and erosions were graded separately in the same categories, and on this third occasion porosis was recorded irrespective of its cause. This is important

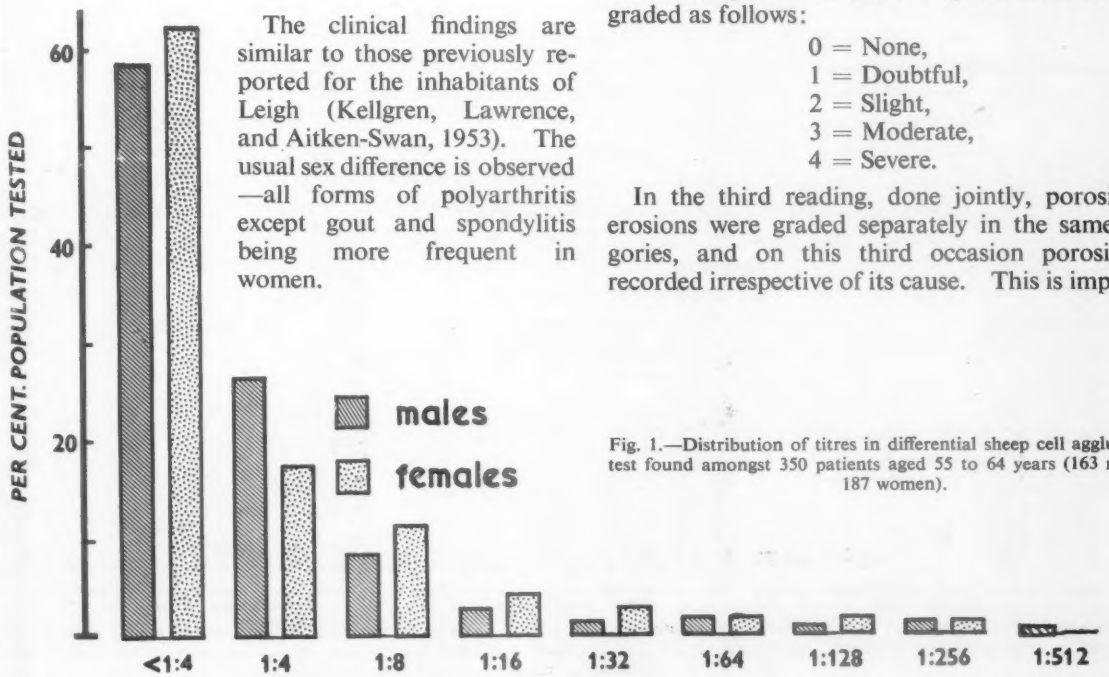


Fig. 1.—Distribution of titres in differential sheep cell agglutination test found amongst 350 patients aged 55 to 64 years (163 men and 187 women).

since the most pronounced porosis was seen in association with fractures, neurological disorders, and other obviously non-rheumatoid conditions, some of which could be recognized from the radiological appearances alone.

A composite score was obtained by adding the first two readings to the score for porosis or erosion, whichever was the highest. A score of 5 or over for the three readings was taken as positive.

Radiological changes of this grade or above were found in the hands and/or feet in seventeen women (8 per cent.) and twelve men (7 per cent.). If we assume that all those not *x* rayed were negative, minimal prevalence rates would be 6 per cent. for each of the two sexes. Although the radiological changes of rheumatoid arthritis are not so easily recognized in the larger limb joints and spine, the cervical spine and larger limb joints are very often affected by this disease. Slight changes in these joints were thought to be too difficult to interpret, but moderate or severe changes were considered worth recording. In the first reading seven individuals in whom the films of hands and feet had a composite score of less than 5 and were therefore classed as negative showed destruction of disks and irregularity of the interfacetal joints in the cervical spine which were thought to be rheumatoid in nature. On re-reading these spinal films two were discarded as probably non-rheumatoid, leaving five individuals with positive films of the cervical spine. Two were men, and of these one had a positive D.A.T. and the other had borderline changes in the hand films and a past history of severe polyarthritis in adult life. Of the three women with moderate changes in the cervical spine, all three had borderline changes in the hand films, and one had a positive D.A.T. and clinical rheumatoid of slight severity, the second gave a history of polyarthritis,

TABLE III

X-RAY SIGNS IN 173 MEN AND 207 WOMEN

Reading	Sex	Grade									
		0		1		2		3		4	
		No.	%	No.	%	No.	%	No.	%	No.	%
Rheumatoid Arthritis (first reading of all joints)	Men	93	*54*	60	*35*	15	*9*	3	*2*	2	*1*
	Women	99	*48*	83	*41*	14	*7*	7	*3·5*	4	*2*
Porosis (hands only) .. .	Men	164	*96*	7	*3*	2	*1*	0	*0*	0	*0*
	Women	125	*60*	45	*21*	31	*15*	4	*2*	2	*1*
Erosions (hands only)	Men	132	*75*	27	*16*	12	*7*	0	*0*	2	*1*
	Women	168	*82*	23	*11*	11	*5*	3	*1·5*	2	*1*

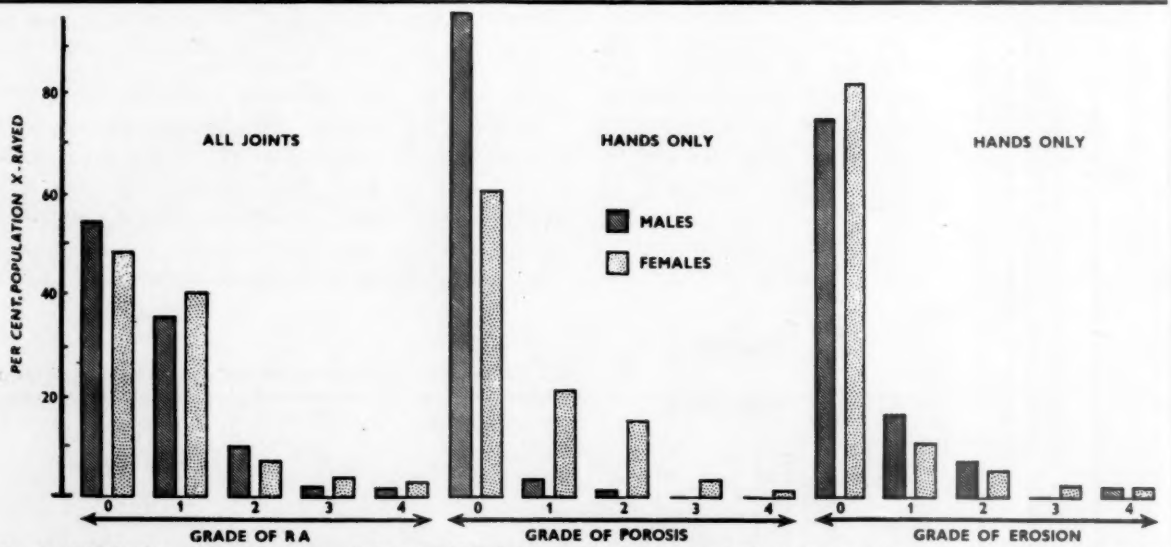


Fig. 2.—Distribution of *x*-ray gradings of rheumatoid arthritis in 380 persons aged 55 to 64 years, by sex, taking the most seriously affected joint in each individual (from first reading of films), and distribution of osteoporosis and erosion in hand films only (from third reading of films).

and the third showed no other evidence of rheumatoid arthritis.

These additional five cases have been considered radiologically positive, bringing the final figure up to twenty women (10 per cent.) and fourteen men (8 per cent.).

The distribution of the *x*-ray changes of rheumatoid arthritis would therefore also appear to be similar in the two sexes in this age group. On the other hand, osteoporosis when read separately appears to be largely confined to women; Table III and Fig. 2 show the distributions by grades of porosis and erosion in the hands based on the results of the third reading of the films, and for comparison the results by grades of rheumatoid changes recorded during the first reading of all the films.

We are well aware of the difficulty of assessing osteoporosis in radiographs of the hands, but the pronounced sex difference observed may well be real and certainly requires further investigation.

Comparison of Clinical, Radiological, and Serological Findings

The association between the clinical gradings of rheumatoid disease and positive *x*-ray findings and/or a positive agglutination test is set out in Table IV and Fig. 3.

Clinical rheumatoid arthritis of moderate or severe degree was found in three men and seven women, and this small group will for simplicity be called the severe group. In one man there was neither serological nor radiological confirmation of the diagnosis, but in the other two men and in all seven women such confirmation was obtained, two men and two women having both a positive D.A.T. and positive *x* rays, four women having positive *x* rays only, and one a positive D.A.T. only.

Clinical rheumatoid arthritis of only slight degree was noted in only two men and in one of these the D.A.T. was positive. By contrast, clinical rheumatoid arthritis of slight degree was noted in 23 women, but in only four was the diagnosis confirmed, twice by *x* ray alone, once by D.A.T. alone, and once by both criteria.

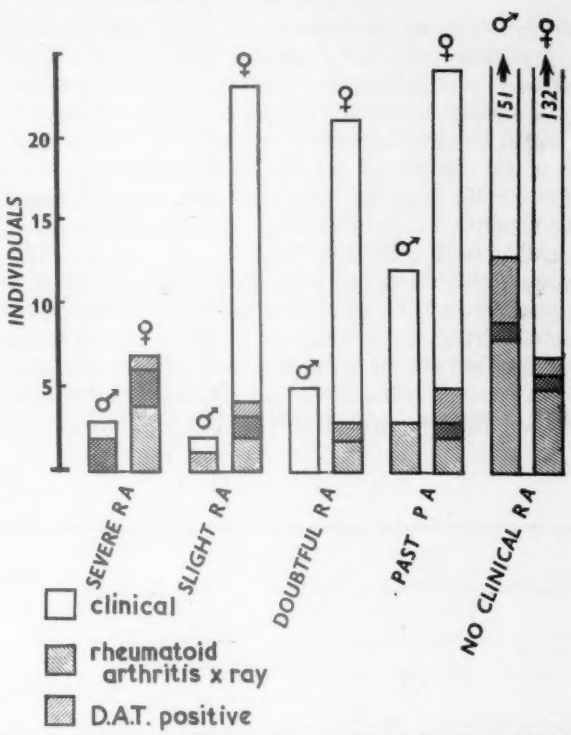


Fig. 3.—Correlation between clinical, radiological, and serological evidence of rheumatoid arthritis in persons *x*-rayed (173 men and 207 women). Columns represent actual number of individuals in each diagnostic group.

Doubtful clinical evidence of rheumatoid arthritis was noted in five men and 21 women. Both *x* rays and D.A.T. were negative in all five men and in eighteen of these women, but two women had positive *x* rays and one a positive D.A.T.

A past history of polyarthritis with no clinical evidence of rheumatoid disease at the time of examination was noted in twelve men and 24

TABLE IV

COMPARISON OF CLINICAL, RADIOLOGICAL, AND SEROLOGICAL EVIDENCE OF RHEUMATOID ARTHRITIS

Clinical Grade	No. of Men					No. of Women				
	X Ray Only	D.A.T. Only	*X* Ray and D.A.T.	*X* Ray and/or D.A.T.	Total	*X* Ray Only	D.A.T. Only	*X* Ray and D.A.T.	*X* Ray and/or D.A.T.	Total
Severe Rheumatoid Arthritis	0	0	2	2	3	4	1	2	7	7
Slight Rheumatoid Arthritis	0	1	0	1	2	2	1	1	4	23
Doubtful Rheumatoid Arthritis	0	0	0	0	5	2	1	0	3	21
Past Polyarthritis	3	0	0	3	12	2	2	1	5	24
No Rheumatoid Arthritis	8	4	1	13	151	5	1	1	7	132
Total	11	5	3	19	173	15	6	5	26	207

N.B.—Of the ten men and twenty women in whom the D.A.T. was not performed, nine men and eighteen women showed no clinical evidence of rheumatoid arthritis, but one of the nine men showed radiological evidence. The remaining three subjects had past polyarthritis or doubtful clinical rheumatoid arthritis and none of these showed radiological evidence of rheumatoid arthritis.

women. Three of these twelve men had positive *x* rays, but none had a positive D.A.T. Of the 24 women, two had positive *x* rays, two had a positive D.A.T., and one was positive by both criteria.

Lastly, there were 151 men and 132 women who were not considered to have any clinical evidence of rheumatoid arthritis. Amongst the 151 men, there were eight with positive *x* rays, four with a positive D.A.T., and one with both. Amongst the 132 women, there were five with positive *x* rays, one with a positive D.A.T., and one with both. Thus, there were thirteen men and seven women presenting radiological and/or serological evidence of rheumatoid arthritis who were recorded as having no clinical rheumatoid arthritis in the opinion of the examiner. The findings in these twenty individuals are set out in Table V. Nearly all of them had either symptoms or clinical findings in the joints which in retrospect might have been at least partly attributed to rheumatoid disease. The fact that no clinical rheumatoid arthritis was recorded may therefore represent only a failure in diagnosis.

When the hands and feet are involved the clinical diagnosis of rheumatoid arthritis is relatively easy, but the diagnosis of rheumatoid arthritis of the larger joints and spine presents great difficulties. At a certain stage of the disease it may be confined to the cervical spine, knees, shoulders, or other limb joints, and clinical diagnosis may be very difficult. This may possibly have been the case in some indivi-

TABLE V

INDIVIDUALS WITH POSITIVE *X* RAY AND/OR D.A.T. RECORDED AS

Case No.	Sex	Age	D.A.T.	Radiological Findings				
				Rheumatoid Arthritis		Osteo-arthritis		
				Grade	Site	Grade	Site	
190	M	57	1/256	None	—	Slight	Hands, feet, spine	Lumbago
191	M	57	1/32	Moderate	Cervical spine	Moderate	Cervical spine	Trivial pa
215	M	55	1/64	Doubtful	Feet	None	—	Recurrent
300	M	60	1/32	None	—	None	—	None
333	M	60	1/64	Doubtful	Hands	Slight	Knees, spine	After cru knees,
W.7	F	64	1/32	Slight	Feet	None	—	3 yrs' pai
14	F	62	1/128	None	—	Slight	Hands, feet	None
55	M	58	1/<4	Slight	Hands	Moderate	Knees, spine, hands	8 yrs' pai at age 4
82	M	62	1/4	Slight	Hands	Slight	Hands	3 yrs' rec
140	M	61	1/<4	Slight	Hands	Slight	Hips, knees, hands	3 yrs' stif
155	M	57	1/<4	Slight	Hands	Slight	Hands, hips, spine	6 yrs' pai age 22
201	M	56	1/<4	Slight	Hands	Moderate	Cervical spine	None
341	M	64	1/8	Slight	Hands	Slight	Hands, knees	6 yrs' rec
372	M	59	—	Slight	Hands	Slight	Spine, left knee	No sympt
378	M	58	1/<4	Slight	Hands	Moderate	Spine	2 yrs' pai
W.22	F	55	1/<4	Slight	Feet	Severe	Hands	10 yrs' pai
180	F	64	1/16	Slight	Hands	Slight	Hands, spine, knees, protrusio acetabuli	5 yrs' pai
194	F	58	1/<4	Slight	Hands	Severe	Hands	20 yrs' kn
226	F	58	1/<4	Slight	Hands	Slight	Cervical spine	5 yrs' ago
277	F	63	1/4	Moderate	Cervical spine	Slight	Hands, feet	10 yrs' pai

duals in Table V, such as Nos. 191, 215, 82, 140, 155, 378, 180. In others there may have been an error in interpretation of *x* rays; this seems likely in No. 372, where there was a past history of fracture, and in Nos. 55, W.22, 194, where there was severe osteo-arthritis. These remarks only serve to remind us of the real difficulties in both clinical and radiological diagnosis in rheumatic disease, especially in slight and atypical cases.

The association between moderate and severe clinical rheumatoid arthritis and a positive *x* ray or D.A.T. is obviously highly significant, but what of the other clinical categories? If we group together past polyarthritis and slight and doubtful clinical rheumatoid arthritis, and compare this group with the individuals recorded as having no clinical evidence of rheumatoid disease, we find that positive *x* rays and positive agglutination tests are both more frequent in this admittedly dubious diagnostic group. The probability of the distribution found being due to chance alone is not great: for positive *x* rays $P<0{\cdot}02$, for positive D.A.T. $P<0{\cdot}05$, for both criteria together $P<0{\cdot}001$.

The association between clinical diagnosis and radiological and serological findings outside the small group of patients with severe typical rheumatoid arthritis is most unsatisfactory, particularly in the men, in whom thirteen of the nineteen with objective criteria were recorded as having no clinical evidence of rheumatoid arthritis.

TABLE V

RECORDED AS HAVING NO CLINICAL RHEUMATOID ARTHRITIS

Symptoms	Clinical Signs of Joint Disease	Clinical Diagnosis
Lumbago one attack; pain in hip	Back, reduced curves, limited motion, vasospasm	Disk degeneration
Trivial pains fingers and toes	One doubtful traumatic Heberden's node	Normal
Recurrent lumbago; few days' pain in arms	Crepitus in shoulders, limited lumbar spine, vaso-spasm, sweating	Osteo-arthritis and disk degeneration
None	Contracture palmar fascia	Dupuytren's contracture
After crush injury to feet, 5 yrs' pains in thumbs, knees, back, feet	Crepitus in knees, tender thickening of lateral metatarso-phalangeal joints	Osteo-arthritis
3 yrs' pain in ankle and neck after sprained ankle	None	Undetermined
None	Heberden's nodes, hallux rigidus, cervical spine limited	Osteo-arthritis
8 yrs' pain and stiffness left knee after severe sciatica at age 43	Left knee very limited and crepitant	Osteo-arthritis (traumatic) and disk degeneration
3 yrs' recurrent back pain after injury	Limited wrists and lumbar spine, fluid and crepitus in knees	Osteo-arthritis and disk degeneration
3 yrs' stiffness right knee; lumbago over 15 yrs ago	Fluid and crepitus in knees, limited elbows, wrists, and spine, vasospasm in extremities	Osteo-arthritis and disk degeneration
6 yrs' pain right knee and thigh; severe lumbago at age 22	Limited spine, right hip and both wrists	Osteo-arthritis and disk degeneration
None	Thickened metacarpo-phalangeal joints, ? limited cervical spine, vasospasm	Normal
6 yrs' recurrent lumbago and sciatica	Limited right elbow and lumbar spine, nodule on elbow	Osteo-arthritis and psychogenic rheumatism
No symptoms; past fracture left wrist and left femur	None	Normal
2 yrs' pain in dorsal region of back and shoulders	Limited cervical and lumbar spine, shoulders painful	Osteo-arthritis and disk degeneration
10 yrs' pain in fingers and knees	Severe Heberden's nodes, limited elbow and right knee	Osteo-arthritis
5 yrs' pain and stiffness hips and knees	Right hip very limited, spine and right knee limited	Osteo-arthritis and disk degeneration
20 yrs' knobbly fingers; no pain	Severe osteo-arthritis fingers, effusion in knee	Osteo-arthritis
5 yrs' ago one attack neuritis right arm	Slight right palmar fascia contracture, vasospasm, sweating	Undetermined
10 yrs' pain left shoulder	Subluxation lateral metatarso-phalangeal joints	Undetermined

Table VI shows the relationship of osteoporosis of the hands in women to clinical rheumatoid arthritis or a positive D.A.T.; four of the seven women with severe clinical rheumatoid arthritis have definite osteo-porosis, 28 of the 177 women without definite clinical rheumatoid arthritis have osteoporosis, and of the 37 women with definite porosis only nine have definite clinical rheumatoid arthritis. In this age group, therefore, only about one-quarter of the osteoporosis recorded as present in the hand films was associated with clinical rheumatoid arthritis, and only one case in eight had a positive D.A.T.

TABLE VI

COMPARISON OF OSTEOPOROSIS IN THE HANDS WITH CLINICAL AND SEROLOGICAL EVIDENCE OF RHEUMATOID ARTHRITIS IN WOMEN

Grade of Porosis		0	1	2	3 & 4	Total
Grade of Clinical Rheumatoid Arthritis	Severe	2	1	1	3	7
	Slight	14	4	5	0	23
	Not definite	109	40	25	3	177
	Total	125	45	31	6	207
Result of D.A.T.	Positive	6	1	3	1	11
	Negative	105	40	25	5	175
	Total	111	41	28	6	186

Comparison with Previous Survey

Detailed comparisons between the findings in the two surveys are not possible, since in 1949-50 only a single diagnosis was recorded, whereas in the present study multiple diagnoses were frequently made. Furthermore, during the lapse of 5 years some individuals had recovered from their old complaints, whilst many others had developed new complaints. Nevertheless, we have reviewed the 24 women and eleven men from the sample *x* rayed in 1954 who were diagnosed as having rheumatoid arthritis on clinical grounds alone in 1949-50.

Women.—In the second study ten of these 24 women were considered to have definite clinical rheumatoid arthritis, four doubtful rheumatoid, and ten no clinical evidence of rheumatoid arthritis.

Of the ten recorded as negative, two were bedfast with obscure painful disorders of the locomotor system which on review were thought to be mainly due to disease of the nervous system, six were considered to have generalized osteo-arthritis, one gave a past history of constitutional illness with swelling of the knees but had no symptoms or signs of arthritis at the time of the second examination, and one gave a past history of severe rheumatic fever at ages 7 and 22, with persistent limb pains, and on examination was found to have a stiff back, abnormal mobility in the joints of the extremities, and radiological signs interpreted as osteo-arthritis in one knee and spondylitis or osteo-arthritis in the sacro-iliac joints.

Men.—The findings in the eleven men were similar: on review in 1954, three were considered to have definite rheumatoid arthritis, six osteo-arthritis, one disk degeneration and past poly-arthritis, and one gave a clinical history of severe polyarthritis in adolescence and now presented with a rigid back, chest expansion of 2 cm., and limitation of movement in hips and shoulders. In this patient spondylitis was diagnosed clinically with some confidence, but *x* rays showed normal sacro-iliac joints, osteo-arthritis of the hips, disk degeneration, and severe Paget's disease.

Severe Cases.—Perhaps the most interesting finding was that of the ten subjects (seven women and three men) recorded as having moderate or severe rheumatoid arthritis in 1954, seven (five women and two men) had been previously diagnosed as having rheumatoid arthritis in 1949-50, while in two of the remaining three the disease had started after the first survey. Thus in only one of these ten severe cases was the diagnosis different, having been recorded as rheumatic fever during the first survey and rheumatoid arthritis during the second.

Clinical Screening Test

Cobb, Warren, Thompson, and Ciocco (1954), and Cobb, Merchant, and Warren (1955) have suggested that morning stiffness might be used as a clinical screening test for rheumatoid arthritis in field surveys. A standard question about morning stiffness was therefore asked during the home interview and again while taking the history before the clinical examination. At the home interview, morning stiffness was recorded as present in 132, and at the clinic interview in 118, but only in 74 individuals was the symptom recorded as positive at both interviews; thus there was a wide difference between observers in recording this characteristic. The association between this symptom and other evidence of rheumatoid arthritis is set out in Table VII (opposite). There appears to be a slight association between morning stiffness as recorded at the clinic and other evidence of rheumatoid arthritis, though this association is not improved by taking only those individuals in whom morning stiffness was recorded at both interviews; also the morning stiffness recorded at the home interview shows virtually no association with other evidence of rheumatoid arthritis. Although morning stiffness is usually pronounced in active rheumatoid arthritis, it may be absent when the disease is in remission in spite of severe anatomical changes in the joints.

TABLE VII

CLINICAL SCREENING TESTS FOR RHEUMATOID ARTHRITIS

Clinical Characteristic	Where Recorded	Positive D.A.T.		Radiological Rheumatoid Arthritis		Clinical Rheumatoid Arthritis		Doubtful Rheumatoid Arthritis or Past Polyarthritis		No Rheumatoid Arthritis		Whole Sample	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Morning Stiffness	Clinic	8	*42*	14	*41*	25	*71*	27	*44*	60	*23*	118	*31*
	Home and Clinic	5	*26*	10	*29*	15	*43*	16	*26*	49	*19*	74	*20*
	Home	5	*26*	16	*47*	17	*49*	28	*45*	103	*39*	132	*35*
Cold Blue Extremities	Clinic	6	*32*	9	*26*	19	*54*	11	*18*	23	*9*	57	*15*
Sweating	Clinic	3	*16*	12	*35*	10	*29*	10	*16*	26	*10*	50	*13*
Tendon Nodules	Clinic	4	*21*	7	*21*	14	*40*	4	*6*	14	*5*	33	*9*
Subcutaneous Nodules	Clinic	3	*16*	4	*12*	6	*17*	4	*6*	0	*0*	11	*3*
Whole Sample		19	*100*	34	*100*	35	*100*	62	*100*	264	*100*	380	*100*

Furthermore, our experience of hospital patients suggests that osteo-arthritis of the large limb joints and disk degeneration may also be associated with morning stiffness, particularly in middle-aged and elderly subjects. In the age group studied, morning stiffness certainly did not appear to provide a useful screening test for rheumatoid arthritis, but it may be more valuable in younger age groups.

Other clinical features such as cold blue extremities, sweating, and tendon nodules in the hands, as recorded at the clinic interview, show some association with rheumatoid disease. Subcutaneous nodules both on the elbows and under the heels were not found in any individuals who had no other evidence of rheumatoid arthritis, but the number of nodules recorded was very small. These three characteristics are clearly found too infrequently to be of any value as screening tests, and the observer error between the home and clinic interviews was even greater than for morning stiffness. As recorded in the clinic interview, these characteristics appear to be reasonably specific, so that cold blue extremities, sweating, and tendon nodules should probably be included in the clinical records as aids to diagnosis.

Discussion

Since the population studied was confined to the 55-64 age group and was drawn exclusively from one town in Lancashire, no general conclusions about prevalence rates can be based on the data presented.

The findings do, however, raise interesting questions about the validity of our diagnostic criteria and of our methods of estimating the prevalence of rheumatoid arthritis in population samples. It would appear that severe typical rheumatoid arthritis involving the hands and feet can be recognized with some certainty, since the individuals with this disease were picked out in both surveys, and in nine out of ten of these cases the clinical diagnosis was confirmed by either a positive D.A.T. or positive *x* ray or both. The significance of a clinical diagnosis of slight and doubtful rheumatoid arthritis or past polyarthritis is questionable, and it seems unlikely that a clinical diagnosis at this level of severity could be made reproducible in the older age groups in which osteo-arthritis and other painful conditions of the limbs are so common. Furthermore, this large diagnostic group of 87 individuals contained only sixteen in whom the diagnosis of rheumatoid arthritis was confirmed by a positive *x* ray and/or D.A.T. These objective findings were, however, significantly more frequent in this vague diagnostic group than in the 283 individuals recorded as having no clinical evidence of rheumatoid arthritis. The degree to which this large but dubious diagnostic group is included will radically alter any estimates of the prevalence of rheumatoid disease, even if cases are accepted only when the *x* ray or D.A.T. is positive, as can be seen from Table VIII and Fig. 4 (overleaf), which show the various prevalence rates for rheumatoid arthritis amongst men and women in the 55-64 age group in Leigh that can be derived from our data. Table VIII shows that comparisons of prevalence rates in different populations would be of little value unless the method of survey were similar and the diagnostic criteria carefully defined.

For practical purposes there appears to be a useful clinical dividing line at "typical rheumatoid arthritis of moderate or great severity affecting the hands and feet". If all cases considered positive by this

TABLE VIII

MINIMAL PREVALENCE OF RHEUMATOID ARTHRITIS BASED ON AVAILABLE SAMPLE OF POPULATION AGED 55–64 YEARS

Clinical Evidence of Rheumatoid Arthritis	Sex							
	Men				Women			
	Total		With Positive *X* Ray and/or D.A.T.		Total		With Positive *X* Ray and/or D.A.T.	
	No.	%	No.	%	No.	%	No.	%
Severe	3	*1·5*	2	*1*	7	*3*	7	*3*
Slight and Severe	5	*2·5*	3	*1·5*	30	*11*	11	*4*
Doubtful, Slight, and Severe	10	*5*	3	*1·5*	51	*18*	14	*5*
All Grades plus Past Polyarthritis	22	*11*	6	*3*	75	*27*	19	*7*
Total *X*-Rayed	173	*85*	19	*9*	207	*75*	26	*9*
Total Available	204	*100*			277	*100*		

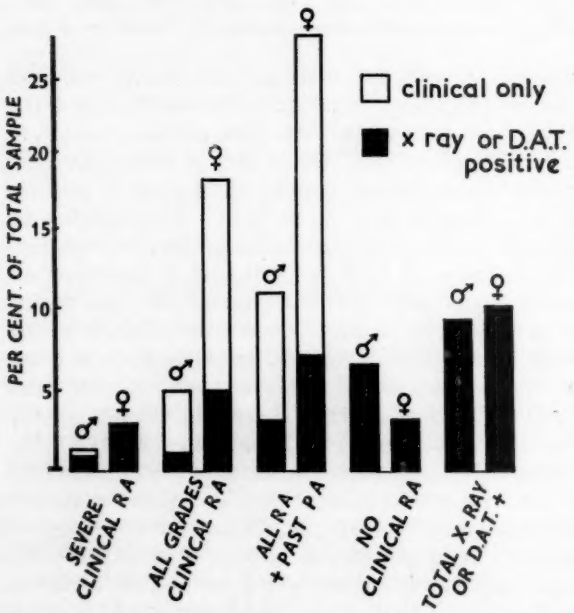


Fig. 4.—Range of minimal prevalence rates for rheumatoid arthritis in 55-64 age group in Leigh, calculated from total available sample of 204 men and 277 women, assuming all individuals not *x*-rayed or tested to be negative.

clinical definition have their hands, feet, and cervical spine *x*-rayed and a D.A.T. performed, a useful objective check can be maintained on the level of clinical diagnosis. Such a method of survey should be useful for screening large populations since at most 3 per cent. of the population would require detailed investigation. This corresponds roughly to the method used by Miall and others (1953), though their clinical dividing line was probably at a lower level of severity and they did not take *x* rays of the cervical spine. This method should give a good indication of the prevalence of rheumatoid disease of the peripheral limb joints, but it could not be used to estimate the prevalence of clinical polyarthritis as a whole, nor could it be used safely to estimate the prevalence of positive *x* ray changes or positive serological tests in the population studied. In our present state of ignorance it would seem essential to study completely small but carefully selected samples of any population under investigation. In such studies clinical, radiological, and serological data should be collected on all individuals in the population sample, whether a clinician thinks they have rheumatoid arthritis or not.

Clinical rheumatoid arthritis as defined by our present diagnostic practice is generally agreed to be about three times as common in women as in men, and the findings in this survey are no exception. However, in this survey radiological signs of rheumatoid arthritis in the hands and feet were found equally in both sexes and the distribution of titres in the D.A.T. was also practically identical. Perhaps the most disturbing finding was that there were thirteen men and seven women with "objective evidence" of rheumatoid disease, namely a positive *x* ray and/or D.A.T., but no clinical evidence. This result could be due to lack of specificity of the radiological and serological findings or to errors of clinical diagnosis. It must be remembered that rheumatoid disease may sometimes affect mainly the central joints and cervical spine or non-articular structures and is then rarely recognized clinically as such, especially under survey conditions. Radiological signs of polyarticular osteo-arthrtis were found more frequently in women than men in this age group, so that the preponderance of clinical polyarthritis in women may well be in some way connected with this greater prevalence of the radiological signs of osteo-arthritis and/or osteoporosis in women. These questions are important for clini-

cal as well as epidemiological work, but more data are required before they can be properly discussed.

Summary

(1) A sample of individuals aged 55-64 years from an urban population were examined clinically, radiologically, and serologically for evidence of rheumatoid arthritis.

(2) Clinical rheumatoid arthritis at all grades of severity was found twice as frequently amongst the women, but the titre values in the sheep cell agglutination test were distributed equally between the sexes. Radiological evidence of rheumatoid arthritis was also found equally in men and women.

(3) In nine out of ten individuals with severe clinical rheumatoid arthritis the diagnosis was confirmed by positive *x* ray and/or agglutination test. With lesser degrees of clinical disease such confirmation became less frequent, and there were twenty individuals with positive *x* rays and/or agglutination tests amongst 283 who were considered to be free from clinical rheumatoid arthritis.

(4) The prevalence rates range from 1 per cent. for men and 3 per cent. for women with severe clinical rheumatoid arthritis confirmed by *x* ray and/or agglutination test to 11 per cent. for men and 27 per cent. for women with all grades of clinical disease including a past history of polyarthritis. Precise diagnostic definition is therefore essential for the study of comparative prevalence rates in different populations.

This work was assisted by a grant-in-aid from the Medical Research Council, and we are particularly grateful to members of the academic and technical staff of the Council's Pneumoconiosis Research Unit for their help in many aspects of the field study and especially in the taking of *x* rays. We owe a special debt to Dr. J. Ball for carrying out all the agglutination tests.

We also wish to thank the Mayor and the Citizens of Leigh for their co-operation, and also the Oakmere Hospital Management Committee for allowing us to use the Walkden Miners' Clinic for part of the survey work.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.

Blécourt, J. J. de (1953). *Rev. Rhum.*, **20**, numéro special, p. 105.

Brooke, E. M. (1953). *Monthly Bull. Minist. Hlth (Lond.)*, **12**, 114.

Cobb, S., Merchant, W. R., and Warren, J. E. (1955). *J. chron. Dis.*, **2**, 50.

——, Warren, J., Thompson, D., and Ciocco, A. (1954). *Penn. med. J.*, **57**, 37.

Edström, G. (1944). *Upsala Läk Fören. Förh.*, **49**, 303.

Kellgren, J. H. (1956). *Annals of the Rheumatic Diseases*, **15**, 55.

——, and Lawrence, J. S. (1952). *Brit. J. industr. Med.*, **9**, 197.

——, ——, and Aitken-Swan, J. (1953). *Annals of the Rheumatic Diseases*, **12**, 5.

——, and Moore, R. (1952). *Brit. med. J.*, **1**, 181.

Lawrence, J. S. (1955). *Brit. J. industr. Med.*, **12**, 249.

Medical Advisory Committee (Scotland) (1945). "Chronic Rheumatic Diseases." H.M.S.O., Edinburgh.

Miall, W. E. (1955). *Annals of the Rheumatic Diseases*, **14**, 150.

——, Caplan, A., Cochrane, A. L., Kilpatrick, G. S., and Oldham, P. D. (1953). *Brit. med. J.*, **2**, 1231.

Ministry of Health (1924). "The Incidence of Rheumatic Diseases," ed. G. Newman. Reports on Public Health and Medical Subjects, No. 23. H.M.S.O., London.

Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 1.

Stocks, P. (1949). "Sickness in the Population in England and Wales in 1944-1947." General Register Office, Studies on Medical and Population Subjects, No. 2. H.M.S.O., London.

Woolsey, T. D. (1952). *Publ. Hlth Rep. (Wash.)*, **67**, 505.

Arthrite rhumatismale dans une population urbaine

RÉSUMÉ

(1) On rechercha les signes d'arthrite rhumatismale chez 481 sujets âgés de 55 à 64 ans d'une population urbaine. Tous furent soumis à l'examen clinique, radiologique et sérologique.

(2) L'arthrite rhumatismale de sévérité variable fut trouvée deux fois plus souvent chez les femmes que chez les hommes, mais les chiffres de la réaction d'agglutination des cellules de mouton furent également repartis entre les deux sexes. De même, un nombre égal d'hommes et de femmes manifesta des signes radiologiques d'arthrite rhumatismale.

(3) Dans 9 cas sur 10 un tableau clinique d'arthrite rhumatismale sévère fut confirmé par la radiographie, par la réaction d'agglutination ou par les deux. Cette confirmation devint plus rare au fur et à mesura que la sévérité clinique de la maladie diminua. Parmi 283 sujets sans manifestations cliniques d'arthrite rhumatismale, il y eut vingt avec des signes radiologiques et/ou sérologiques.

(4) La fréquence de l'arthrite rhumatismale sévère confirmée radiologiquement et/ou sérologiquement fut de 1% pour les hommes et de 3% pour les femmes, tandis que le pourcentage des cas avec toutes les formes cliniques, y compris ceux avec des antécédants personnels de polyarthrite, fut 11% et 27% respectivement. Une définition diagnostique précise est donc essentielle pour étudier la fréquence comparée de la maladie dans de différentes populations.

Artritis reumatoide en una población urbana

SUMARIO

(1) Se investigaron las manifestaciones de artritis reumatoide en 481 sujetos de 55 a 64 años de edad, de una población urbana. Todos ellos fueron sometidos al examen clínico, radiológico y sérologico.

(2) La artritis reumatoide de severidad variable fué encontrada dos veces más a menudo en mujeres que en hombres, pero las cifras de la reacción de aglutinación de células de oveja se repartieron igualmente entre cada sexo. Asímismo, un número igual de hombres y de mujeres tuvo manifestaciones radiológicas de artritis reumatoide.

(3) Sobre 10 casos de artritis reumatoide clínicamente severa, 9 presentaron una confirmación radiológica, serológica o ambas. Tal confirmación fué más rara en casos más benignos. Entre 283 sujetos sin manifestaciones clínicas de artritis reumatoide hubo veinte con signos radiológicos, serológicos o ambos.

(4) La frecuencia de la artritis reumatoide severa y confirmada radiológica y/o serológicamente fué de 1% de los hombres y de 3% de las mujeres, mientras que el percentaje de los casos con todas las formas clínicas, incluyendo aquellos con antecedentes personales de poliartritis, fué de 11% y de 27% respectivamente. Una definición diagnóstica precisa es ,pués, esencial para estudiar la frecuencia comparada de la enfermedad en diferentes poblaciones.

Ann. rheum. Dis. (1956), **15**, 12.

NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS
II. SURVIVAL OF TRANSFUSED ERYTHROCYTES IN PATIENTS WITH RHEUMATOID ARTHRITIS

BY

W. R. M. ALEXANDER, J. RICHMOND, L. M. H. ROY, AND J. J. R. DUTHIE

From the Rheumatic Unit, Northern General Hospital, Edinburgh

(RECEIVED FOR PUBLICATION JULY 11, 1955)

In a recent report, Roy, Alexander, and Duthie (1955) reviewed the literature on the characteristics of anaemia in rheumatoid arthritis and described abnormalities of iron metabolism in this disease. It was shown that the anaemia did not present the typical features of iron-deficiency and that there was no evidence of impaired absorption of iron from the gut in the majority of cases. Decreased survival of erythrocytes transfused from healthy donors to patients with active rheumatoid arthritis had been observed, and it was suggested that a reduced life-span of the patient's own red cells might be a factor in the production of anaemia.

There are few reports on the fate of transfused red cells in rheumatoid arthritis. Brown, Hayward, Powell, and Witts (1944) found that cell survival was normal in one patient with "severe disease". It was not made clear if this implied that evidence of active inflammation was still present. Mollison and Paterson (1949) gave two transfusions to each of two patients suffering from rheumatoid arthritis. Cells used for the first transfusion in each case were incubated *in vitro* with serum containing Rh-blocking antibody and in both instances survival of the transfused cells was markedly reduced. Both patients were transfused again with cells which had not been exposed to blocking antibody. In one case rapid destruction was again observed, but in the other, cell survival was of normal duration.

Since the start of the present investigation two further reports have appeared. Freireich, Ross, Bayles, Emerson, and Finch (1954) measured the survival of transfused cells in patients with rheumatoid arthritis and found it to be decreased, destruction being most marked in patients with active disease. Bunim (1954), who used ^{51}Cr. to measure the survival of patient's own red cells, stated that an increased rate of destruction was recorded in patients with active rheumatoid arthritis.

The present study was designed to investigate more thoroughly the possibility that abnormal destruction of red cells might be a factor in the causation of anaemia in rheumatoid arthritis. The first part of the report deals with studies of the survival of cells from healthy donors in patients with active disease and varying degrees of anaemia.

It was felt that abnormally rapid destruction of healthy red cells might not necessarily imply that the patients' own red cells were being destroyed at the same rate. The second part of the report records the results of experiments designed to compare the survival of cells from a rheumatoid patient with that of cells from a healthy donor in the same recipient; recipients with clear-cut evidence of active rheumatoid disease were closen. Such a comparison does not provide any measure of the life-span of the recipient's own red cells, but it was considered important to ascertain whether any difference existed between the survival of healthy cells and rheumatoid cells in the rheumatoid patient.

In addition, a comparison has been made of the survival of healthy red cells before and during the administration of ACTH to rheumatoid patients. Similar observations have been recorded before and during haematological improvement induced by the administration of iron by the intravenous route.

Materials and Methods

Recipients.—Nineteen patients were selected for transfusion. All were under treatment as in-patients and suffered from well-established rheumatoid disease involving many joints. All were in an active phase of the disease with a raised erythrocyte sedimentation rate and varying degrees of anaemia. Details of age, sex, and duration of disease are included in Table I (opposite) and Table II (overleaf).

During the period of investigation all patients underwent a basic regime of treatment consisting of general rest, splinting of painful joints, analgesics, and physiotherapy.

Transfusions were given to two healthy males as a control on the technique employed.

Donors.—Normal blood of Group O and suitable rhesus group was supplied by the Blood Transfusion Service, Royal Infirmary, Edinburgh.

Blood from rheumatoid donors was obtained from volunteers among the patients in the Rheumatic Unit, Northern General Hospital, Edinburgh. The criteria for selection of donors were as for recipients, but only individuals with moderate degrees of anaemia (more than 75 per cent. Hb) were asked to donate blood.

Storage of Blood before Transfusion.—Blood was stored at 4° C. in acid-citrate-dextrose for 48 hrs after withdrawal. Red cells were packed within 2 hrs of transfusion. Direct compatibility tests were made by the Blood Transfusion Service.

Technique for Measurement of Survival of Transfused Red Cells.—The differential agglutination technique evolved by Ashby (1919) was used with certain modifications.

To 1 ml. physiological saline was added 20 c.mm. capillary blood obtained by ear prick. 0·3 ml. of this suspension was mixed with an aliquot of appropriate antiserum (undiluted) in a 75 × 10 mm. test tube and kept at room temperature for 1 hr. The suspension was centrifuged at 1,000 r.p.m. for 1 min. and thereafter tapped gently until the agglutinate was released from the bottom of the tube and an even suspension in the supernate obtained. A sample of the supernate was removed with a Pasteur pipette and the number of free red cells counted in a Neubauer chamber.

All recipients belonged to blood groups A, B, or AB, with one exception (in which Anti-D serum was used to measure survival of Group O Rh-negative cells in a Group O Rh-positive recipient). Potent Anti-A or Anti-B sera, supplied by the Blood Transfusion Officer, were used to produce agglutination of the recipient's cells. Before transfusion the appropriate anti-serum was tested on at least two occasions with the cells of the prospective recipient. A free cell count after agglutination of 10,000/c.mm. or less was considered satisfactory.

Where possible, surviving cells were counted at daily intervals for 4 days after transfusion. Subsequent counts were made approximately twice weekly. The number of surviving cells was expressed as a percentage of the highest count recorded during the first 4 days. Survival was measured from the day on which this count was recorded.

Haemoglobin Concentration (Hb) was measured in a colorimeter as alkali haematin. Results are expressed as percentages of 14·8 g./100 ml. whole blood.

Erythrocyte Sedimentation Rate (E.S.R.) was measured in Westergren tubes. Dry ammonium/potassium oxalate mixture was used as an anti-coagulant.

Results

Survival of Red Cells from Healthy Donors in Patients suffering from Active Rheumatoid Arthritis.—Details of the age, sex, and clinical status of the eighteen patients before transfusion are included in Table I.

TABLE I

SURVIVAL OF CELLS FROM HEALTHY DONORS IN EIGHTEEN PATIENTS WITH RHEUMATOID ARTHRITIS

Case No.	Age	Sex	Duration of Disease (yrs)	Before Transfusion		Volume Transfused (pints)	Mean Survival Time (days)
				Hb (per cent.)	E.S.R. (mm./hr)		
1	75	F	1	73	104	2	16·4
2	48	F	12	62	52	2	19·7
3	52	M	4	60	37	2	17·9
4	60	M	2	52	124	2	7·8
5	65	F	8	68	60	1	21·9
6	52	F	1	53	33	2	18·1
7	46	F	16	50	33	2	19·7
8	53	F	15	66	62	2	16·3
9	40	F	30	61	64	2	20·8
10	43	F	3½	72	75	2	5·3
11	51	F	1½	74	81	2	22·7
12	38	F	4	70	34	2	16·9
13	57	F	5	79	19	1	17·6
14	59	M	3	87	34	2	21·6
15	58	F	3	53	53	1	25·4
16	79	F	6	58	76	2	13·7
17	51	F	1	72	85	2	21·3
18	45	F	5	63	72	3	14·0
			Mean ..	63	61		

Average of mean survival times: 17·6 days. Standard deviation: 4·88.

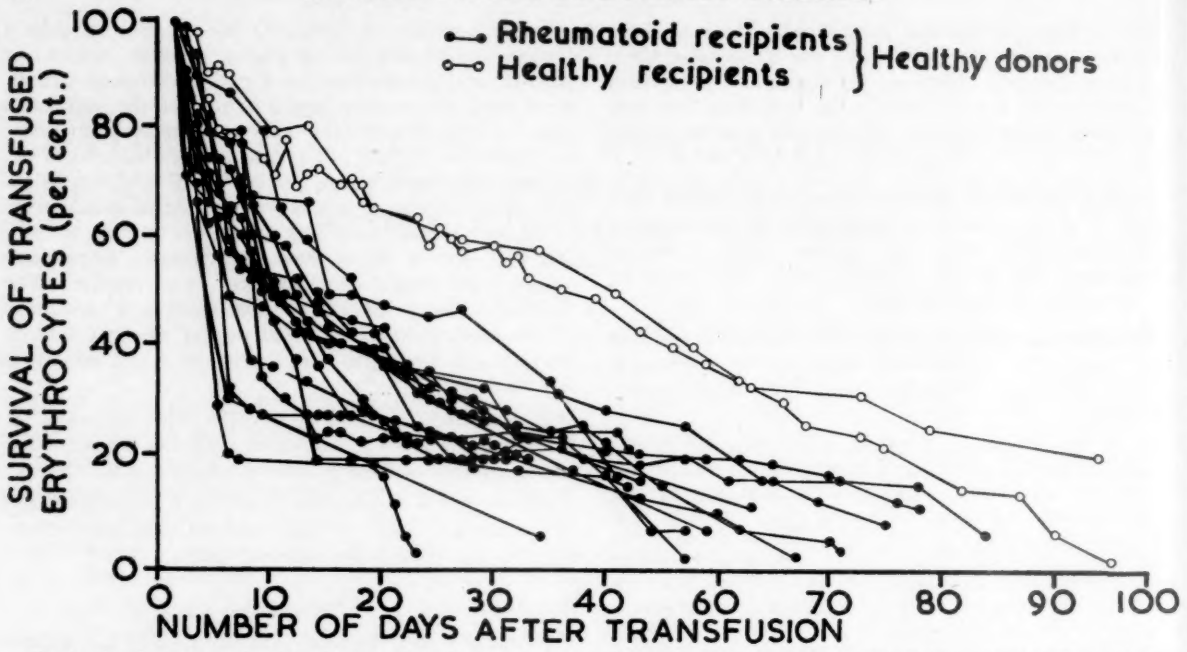


Fig. 1.—Survival of transfused erythrocytes from healthy donors in eighteen patients with rheumatoid arthritis and two healthy controls.

Fig. 1 presents a composite graph showing the rate of elimination of cells transfused from healthy donors to these recipients. The results in two healthy controls are included for comparison. Twelve of the patients were transfused on more than one occasion, but the data given in Fig. 1 refer only to the first transfusion. The nineteenth patient in the series is omitted from Table I and Fig. 1 as rheumatoid cells were given in the first transfusion.

The initial loss of transfused cells in the rheumatoid recipients was abnormally rapid in all cases. Subsequently the rate of destruction became more linear in character, resembling that seen in the controls. The duration of survival of transfused cells was calculated from the formulae evolved by Brown and others (1944). The figures for mean survival time correspond to the "average life ($\bar{t}$ days)" used by these authors. In six cases of idiopathic hypochromic anaemia investigated by them the average life ($\bar{t}$ days) ranged from 38·2 to 53·9 with a mean of 44·8. The mean survival time for each patient is shown in Table I. The average of the means was 17·6 with a standard deviation of 4·88.

No clear relationship between the disappearance rate and the initial degree of anaemia was found,

TABLE II

COMPARISON OF SURVIVAL OF CELLS FROM HEALTHY AND RHEUMATOID DONORS TRANSFUSED TO SEVEN RHEUMATOID RECIPIENTS (GROUP I)

Case No.	Age	Sex	Duration of Disease (yrs)	Before 1st Transfusion		Volume Transfused (pints)	Donor	Mean Survival Time (days)	Before 2nd Transfusion		Volume Transfused (pints)	Donor	Mean Survival Time (days)
				Hb (per cent.)	E.S.R. (mm./hr)				Hb (per cent.)	E.S.R. (mm./hr)			
1	75	F	1	73	104	2	Healthy	16·4	65	89	1	Rheumatoid	25·8
2	48	F	12	62	52	2	Healthy	19·7	68	32	1	Rheumatoid	34·1
3	52	M	4	60	37	2	Healthy	17·9	82	24	1	Rheumatoid	29·1
4	60	M	2	52	124	2	Healthy	7·8	64	118	1	Rheumatoid	22·9
5	65	F	8	68	60	1	Healthy	21·9	65	81	1	Rheumatoid	32·1
18	45	F	5	63	72	3	Healthy	14·0	77	61	1	Rheumatoid	37·8
19	50	M	2	77	22	1	Rheumatoid	41·4	75	71	1	Healthy	20·7
			Mean	65	67			Mean	71	68			

Average of mean survival times: healthy cells, 16·9 days; rheumatoid cells, 31·9 days.

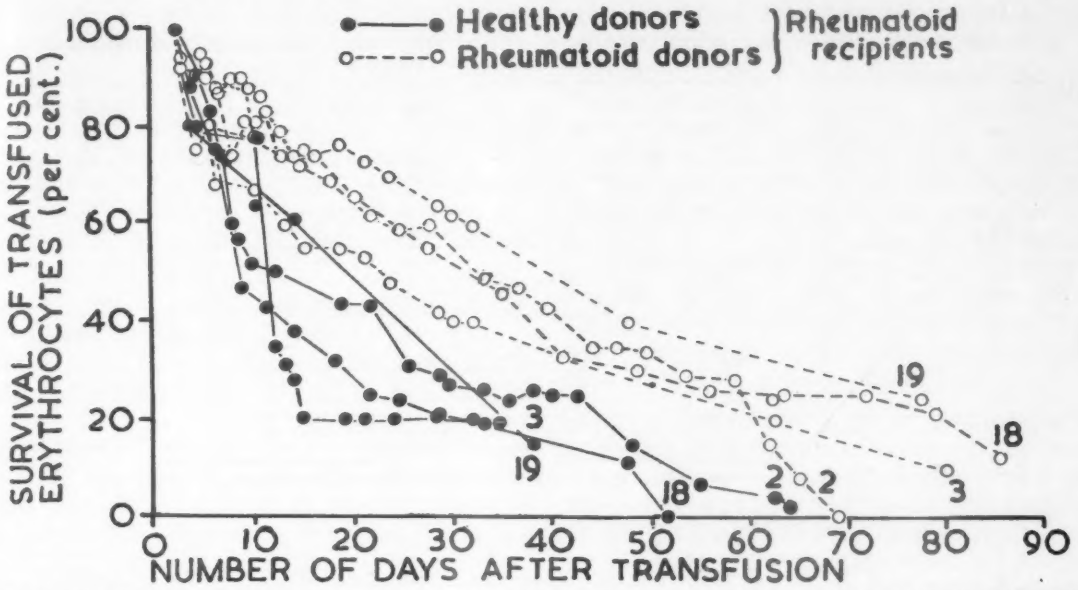


Fig. 2.—Survival of transfused erythrocytes from both healthy and rheumatoid donors in each of four patients with rheumatoid arthritis. (Cases 2, 3, 18, 19).

but in five patients (Cases 1, 4, 9, 10, and 16), where the erythrocyte sedimentation rate before transfusion was 64 mm./hr or more, 50 per cent. of transfused cells had been destroyed in 6 days or less, suggesting a relationship between the activity of the disease and the rate of destruction of transfused cells.

Fourteen patients received cells from 2 pints of blood, three received cells from 1 pint of blood, and the remaining patient was given cells from 3 pints of blood. The number of red cells transfused did not appear to influence the total duration of survival or the shape of the curves recorded in this group of patients.

Comparison of Survival of Red Cells from Healthy Donors and Rheumatoid Donors in Individual Patients

Group I.—Seven patients received two transfusions, one from a healthy and one from a rheumatoid donor. One patient (No. 19) received cells from a rheumatoid donor first; the other six received healthy cells before rheumatoid cells.

Table II includes details of the age, sex, and clinical status of the seven recipients in Group I. Elimination rates of cells from healthy and rheumatoid donors in four of these patients are given in Fig. 2. For the sake of clarity comparative curves obtained from the other three patients in the group have been omitted, but the curves in all seven have been analysed and will be discussed below. In all seven patients the initial destruction of transfused cells was less rapid when rheumatoid cells were given, although strictly normal linear decay was not observed.

Mean survival times following the first and second transfusions is shown in Table II. The average of the mean survival times following the transfusion of cells from healthy donors was 16·9 days in contrast to that following the transfusion of cells from rheumatoid donors which was 31·9 days. The difference between the averages was 15. The standard error of the difference was 3·07 $\left(\frac{\text{Difference}}{\text{S.E. of Difference}} = 4{\cdot}88;\ P<0{\cdot}01\right)$. The difference is therefore highly significant.

Group II.—It might be argued that the more prolonged survival of the cells from rheumatoid donors could be accounted for by improvement in the clinical condition of the recipients following the first transfusion from healthy donors. To test this possibility seven other patients were given two consecutive transfusions from healthy donors. Details of the clinical status of patients before each transfusion are given in Table III (overleaf). The average mean survival time after the first transfusion was 17·1 days; after the second transfusion it was 21·9 days. The difference between the averages was 4·8. The standard error of difference was 4·30 $\left(\frac{\text{Difference}}{\text{S.E. of Difference}} = 1{\cdot}11;\ P>0{\cdot}05\right)$. The difference was not significant.

As an additional check the average mean survival time following a total of 26 transfusions of healthy cells to nineteen rheumatoid recipients was calculated and was found to be 19·1 days $\pm$ 1·3. The figure of 16·9 days in Group I is therefore representative of the whole series.

In two patients in Group II (Cases 6 and 9) survival following the second transfusion was significantly prolonged; 18·1 to 33·6 days and 20·8

TABLE III

COMPARISON OF SURVIVAL OF CELLS FROM HEALTHY DONORS AFTER TWO TRANSFUSIONS TO SEVEN RHEUMATOID RECIPIENTS (GROUP II)

Case No.	Age	Sex	Duration of Disease (yrs)	Before 1st Transfusion		Volume Transfused (pints)	Mean Survival Time (days)	Before 2nd Transfusion		Volume Transfused (pints)	Mean Survival Time (days)
				Hb (per cent.)	E.S.R. (mm./hr)			Hb (per cent.)	E.S.R. (mm./hr)		
6	52	F	1	53	33	2	18·1	79	43	2	33·6
7	46	F	16	50	33	2	19·7	75	20	2	13·2
8	53	F	15	66	62	2	16·3	74	47	2	15·6
9	40	F	30	61	64	2	20·8	61	12	2	37·5
10	43	F	3½	72	75	2	5·3	64	125	2	11·2
11	51	F	1½	74	81	2	22·7	90	25	1	23·4
12	38	F	4	70	34	2	16·9	82	26	2	18·6
			Mean ..	64	55		Mean ..	75	42		

Average of mean survival times: after 1st transfusion, 17·1 days; after 2nd transfusion, 21·9 days

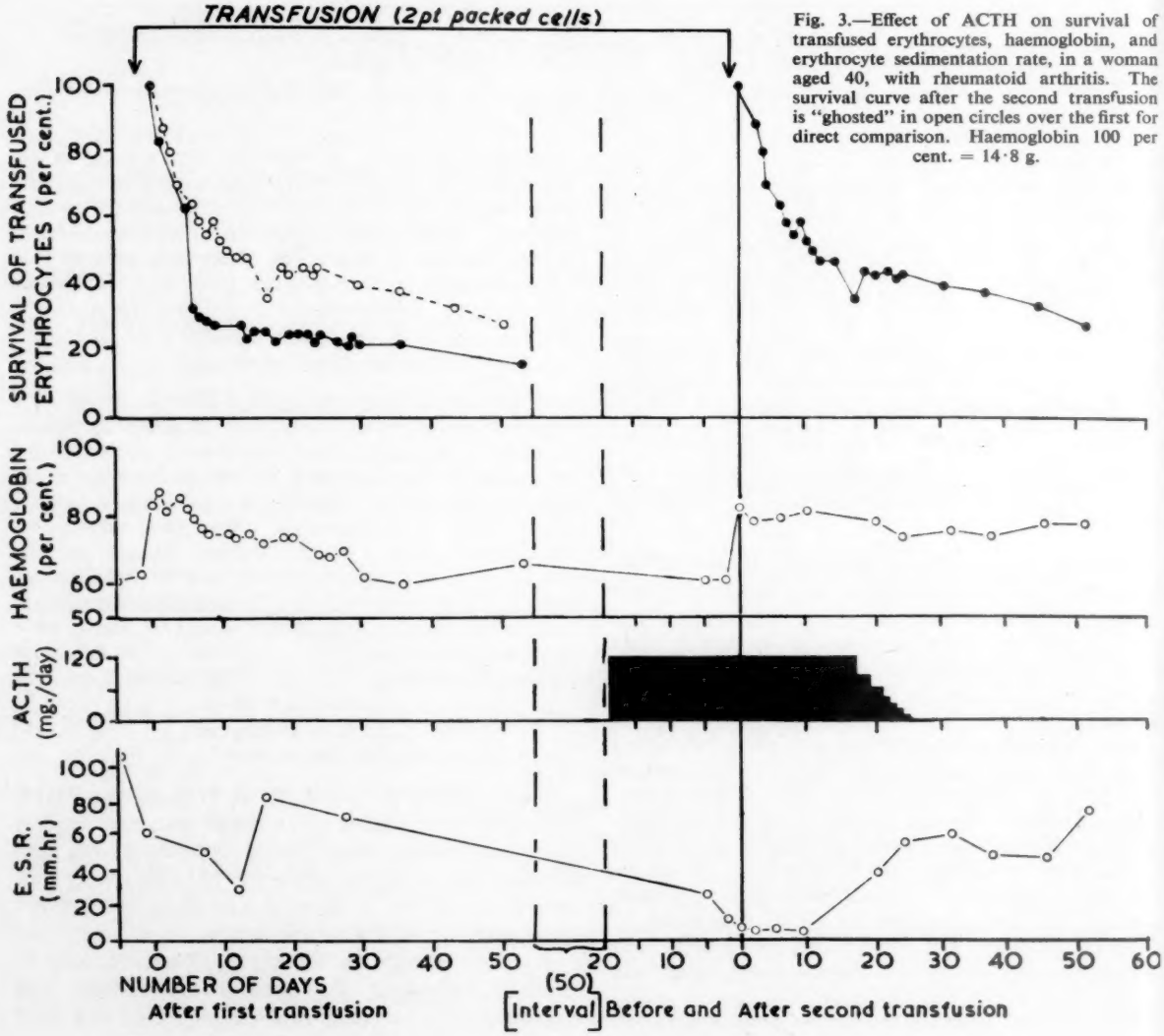


Fig. 3.—Effect of ACTH on survival of transfused erythrocytes, haemoglobin, and erythrocyte sedimentation rate, in a woman aged 40, with rheumatoid arthritis. The survival curve after the second transfusion is "ghosted" in open circles over the first for direct comparison. Haemoglobin 100 per cent. = 14·8 g.

to 37·5 days respectively. In one patient (Case 6) the haemoglobin level had risen from 53 to 79 per cent. following the first transfusion, but there was no significant change in the erythrocyte sedimentation rate. In the second patient (Case 9), although the haemoglobin level was unchanged, the erythrocyte sedimentation rate had fallen from 64 to 12 mm./hr after the first transfusion. The results in these two patients do not alter the significance of the findings in the group as a whole.

Effect of ACTH on Survival of Red Cells transfused from Healthy Donors.—Two patients belonging to Group II were given suppressive doses of ACTH before the second transfusion of cells from healthy donors.

Fig. 3 shows the survival curves after each transfusion in the first patient. Although adequate clinical suppression was attained and the erythrocyte sedimentation rate became normal just before the second transfusion, the initial disappearance rate of the transfused cells was equally rapid after both transfusions. The slope of elimination became less steep on the tenth day after the second transfusion, but the overall shape was unaltered.

In the second patient to whom ACTH was administered, complete suppression of signs of the disease was not achieved with the dose given. The erythrocyte sedimentation rate did not return to normal although the patient was free from symptoms (Fig. 4). Disappearance of cells after the first transfusion was very rapid and after the second the rate was not materially altered by the administration of ACTH.

Effect of Intravenous Iron on Survival of Cells transfused from Healthy Donors.—Three patients in Group II were given 2 g. saccharated oxide of iron intravenously before the second transfusion. The iron was administered to one patient immediately before transfusion and no prolongation of cell survival was observed.

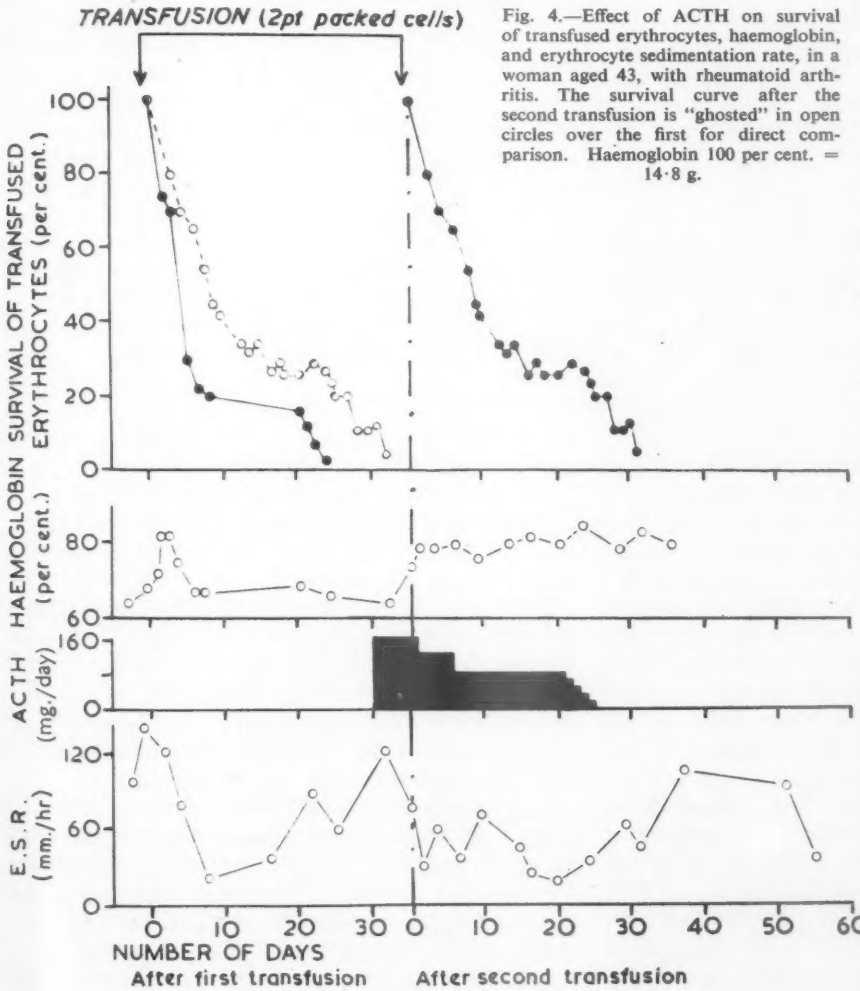


Fig. 4.—Effect of ACTH on survival of transfused erythrocytes, haemoglobin, and erythrocyte sedimentation rate, in a woman aged 43, with rheumatoid arthritis. The survival curve after the second transfusion is "ghosted" in open circles over the first for direct comparison. Haemoglobin 100 per cent. = 14·8 g.

In the other two patients the second transfusion was delayed until haematological improvement had occurred. In one of these (Fig. 5, overleaf) the haemoglobin had risen from 50 to 75 per cent. in 60 days. The other (Fig. 6, overleaf) showed only moderate improvement after iron administration; although the red cell count rose by 1·2 million/c.mm., the haemoglobin only increased by 8 per cent. In neither patient was cell survival prolonged after the second transfusion.

Discussion

The results of this investigation have shown that, in active rheumatoid arthritis, the rate of elimination from the circulation of red cells transfused from healthy donors is abnormal. The initial disappearance of healthy cells is rapid, elimination thereafter approximating to the linear mechanism of normal senescence. When cells from rheumatoid

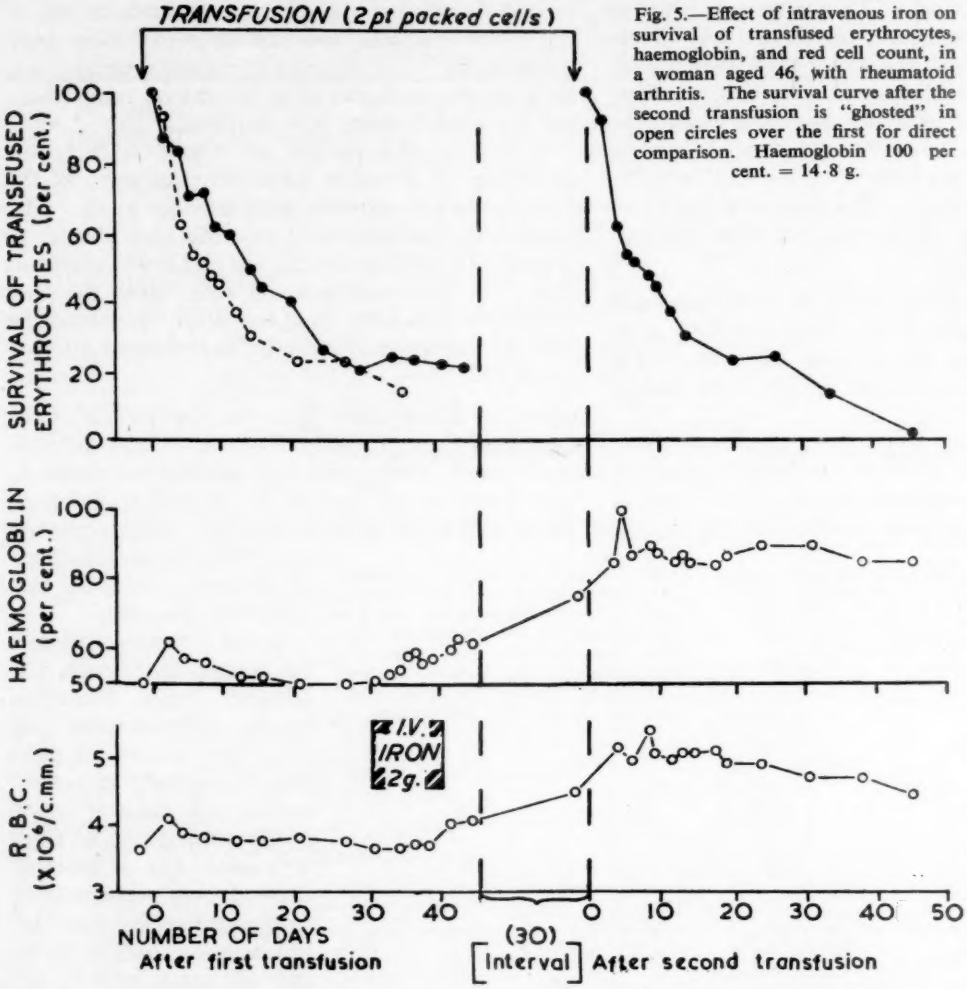


Fig. 5.—Effect of intravenous iron on survival of transfused erythrocytes, haemoglobin, and red cell count, in a woman aged 46, with rheumatoid arthritis. The survival curve after the second transfusion is "ghosted" in open circles over the first for direct comparison. Haemoglobin 100 per cent. = 14·8 g.

patients are transfused, overall elimination is less rapid and initial disappearance more gradual.

These results suggest that increased cell destruction may be one factor in the causation of anaemia in rheumatoid arthritis, but, in view of the persistent hypochromia of the red cells and the absence of clinical evidence of haemolysis, it is unlikely that this is the only factor concerned. Accurate interpretation of Ashby curves is difficult, but the rapid initial elimination of healthy cells, followed by almost linear decay, might be explained by an increased susceptibility to destruction of a proportion of the transfused cells. Such susceptibility could only be "acquired" after transfusion and would suggest the presence of a sensitizing agent in the circulation of the recipient which is taken up by a proportion of the transfused cells. In these circumstances the unsensitized cells would be eliminated by normal senescence. The normal survival of rheumatoid cells in healthy recipients reported by Freireich and others (1954) does not exclude this possibility, as Loutit and Mollison (1946) have shown that red cells from four patients suffering from acquired haemolytic anaemia survived normally in healthy recipients.

Overactivity of the reticulo-endothelial system could account for increased red cell destruction. There is reason to believe, from pathological studies and from recent experiments with intravenous iron, that the reticulo-endothelial system is overactive in rheumatoid arthritis. Such a state of affairs cannot explain the difference in the rate of elimination of healthy and rheumatoid cells in the rheumatoid patient unless at the same time it is postulated that cells from patients with rheumatoid arthritis are less susceptible to destruction than cells from healthy donors.

Detailed studies of red cells from rheumatoid patients are in progress, with the aim of defining any physical or immunological characteristics which might explain their ability to survive longer than normal red cells in the circulation of patients with rheumatoid arthritis, but at the moment no explanation of this phenomenon can be offered.

The administration of short courses of ACTH in doses sufficient to control clinical symptoms has not materially influenced the survival of cells transfused from healthy donors. This would suggest that the factor or factors responsible for decreased survival are not directly influenced by adrenal stimulation.

Improvement in the blood picture after the

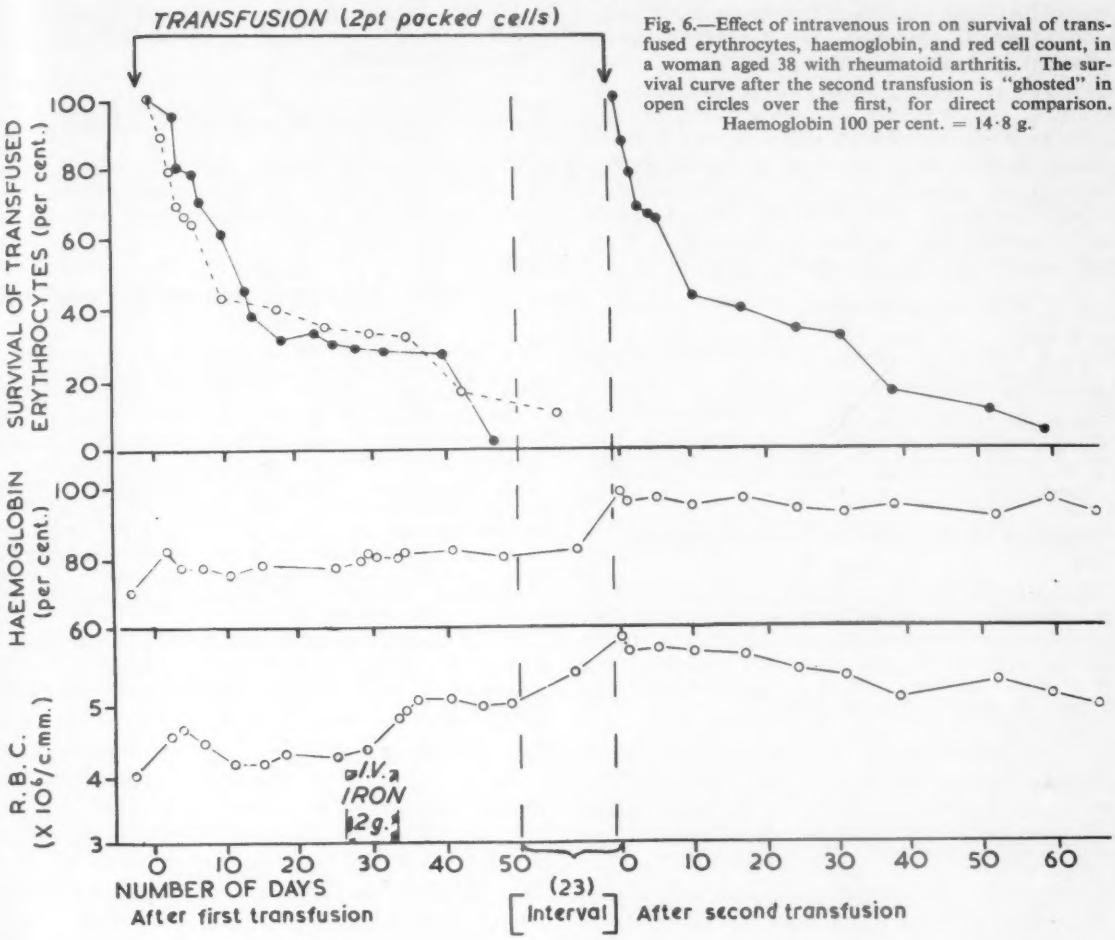


Fig. 6.—Effect of intravenous iron on survival of transfused erythrocytes, haemoglobin, and red cell count, in a woman aged 38 with rheumatoid arthritis. The survival curve after the second transfusion is "ghosted" in open circles over the first, for direct comparison. Haemoglobin 100 per cent. = 14·8 g.

administration of intravenous iron has not been followed by more prolonged survival of normal cells in these patients.

It would appear that more than one mechanism may be responsible for the production of anaemia in rheumatoid arthritis. Hypochromia of the red cells may arise from defective synthesis of haemoglobin in the marrow, which may be related to the abnormal metabolism of iron. Reduction in the red cell count may be due in part at least to increased destruction of the patient's own erythrocytes by cells of the reticulo-endothelial system.

Summary

(1) Erythrocytes from healthy donors are eliminated from the circulation with abnormal rapidity in patients suffering from rheumatoid arthritis.

(2) Erythrocytes from rheumatoid donors survive longer in rheumatoid recipients than cells from healthy donors.

(3) Consecutive transfusions from healthy donors do not as a rule influence the speed with which these cells are destroyed in patients with rheumatoid arthritis.

(4) The administration of ACTH in doses sufficient to suppress the clinical signs of the disease does not prolong the survival of normal erythrocytes in rheumatoid recipients.

(5) Haematological improvement after the administration of intravenous iron is not accompanied by increased survival of normal erythrocytes in rheumatoid recipients.

We wish to record our sincere gratitude to Dr. R. A. Cumming, Blood Transfusion Service, Edinburgh Royal Infirmary, who supplied blood from healthy donors and anti-sera for differential agglutination. He also made himself responsible for direct cross-matching of blood from donors and recipients, and was available at all times with expert advice. We also wish to express our thanks to Dr. P. E. Brown, of the Department of Public Health

and Social Medicine, Edinburgh University, for statistical help, and to Miss Jane Hurst and Miss Dorothy Anderson, haematological technicians, Rheumatic Unit, for their accurate and painstaking work throughout the investigation.

Throughout the period when this work was done, the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company. One of us (W.R.M.A.) was the holder of the Hastilow Research Scholarship in Rheumatism, awarded by the University of Edinburgh.

REFERENCES

Ashby, W. (1919). *J. exp. Med.*, **29**, 267.
Brown, G. M., Hayward, O. C., Powell, E. O., and Witts, L. J. (1944). *J. Path. Bact.*, **56**, 81.
Bunim, J. J. (1954). *Annals of the Rheumatic Diseases*, **13**, 365.
Freireich, E. J., Ross, J. F., Bayles, T. B., Emerson, C. P., and Finch, S. C. (1954). *Ibid.*, **13**, 365.
Loutit, J. F., and Mollison, P. L. (1946). *J. Path. Bact.*, **58**, 711.
Mollison, P. L., and Paterson, J. C. S. (1949). *J. clin. Path.*, **2**, 109.
Roy, L. M. H., Alexander, W. R. M., and Duthie, J. J. R. (1955). *Annals of the Rheumatic Diseases*, **14**, 63.

Nature de l'anémie dans l'arthrite rhumatismale

RÉSUMÉ

(1) Les érythrocytes des donneurs sains sont éliminés de la circulation avec une vitesse anormale chez des malades atteints d'arthrite rhumatismale.

(2) Les érythrocytes des donneurs rhumatismaux survivent plus longtemps que les globules des donneurs sains chez les réceveurs rhumatismaux.

(3) Des transfusions consécutives de donneurs sains n'influencent pas d'ordinaire la vitesse de la destruction chez les rhumatisants.

(4) L'administration de l'ACTH en doses suffisantes pour supprimer les signes cliniques de la maladie ne prolongent pas la vie des érythrocytes normaux chez les réceveurs rhumatisants.

(5) L'amélioration hématologique après l'administration intraveineuse de fer ne s'accompagne pas d'une prolongation de la vie des globules rouges normaux chez les réceveurs rhumatisants.

Naturaleza de la anemia en la artritis reumatoide

SUMARIO

(1) Los eritrocitos de los dadores sanos se eliminan de la circulación con una velocidad anormal en enfermos con artritis reumatoide.

(2) Los eritrocitos de los dadores reumáticos sobreviven más tiempo que los glóbulos de los dadores sanos en los receptores reumáticos.

(3) Transfusiones consecutivas de dadores sanos no afectan generalmente la velocidad de la destrucción en los reumáticos.

(4) La administración de la ACTH en dosis suficientes para suprimir las manifestaciones clínicas de la enfermedad no prolonga la vida de los eritrocitos normales en los receptores reumáticos.

(5) La mejoría hematológica después de la administración endovenosa de hierro no se acompaña de una prolongación de la vida de los eritrocitos en los receptores reumáticos.

Ann. rheum. Dis. (1956), **15**, 21.

KERATO-CONJUNCTIVITIS SICCA AND RHEUMATOID ARTHRITIS

BY

MALCOLM THOMPSON* AND STELLA EADIE

From the Rheumatic Unit, Northern General Hospital, Edinburgh, and the Edinburgh Royal Infirmary

(RECEIVED FOR PUBLICATION OCTOBER 13, 1955)

Although the ophthalmic lesions which constitute kerato-conjunctivitis sicca have long been known, the nature of the condition has remained obscure. Duke-Elder (1930) reviewed those rare cases in which lesions of the lacrimal secretory nerves or of the gland parenchyma (including congenital aplasia, surgical extirpation, infiltrations by sarcoid, leukaemic or malignant tissue) resulted in deficient lacrimal secretion and the subsequent development of corneal and conjunctival lesions of the sicca type. These rare cases, however, accounted for only a small proportion of all the patients suffering from kerato-conjunctivitis sicca, and in the majority no local ophthalmic cause for deficient lacrimation and sicca lesions could be found.

Sjögren (1933) described in detail his observations on eighteen patients with idiopathic kerato-conjunctivitis sicca and drew attention to its frequent association with such clinical features as polyarthritis, xerostoma, and salivary gland enlargement, occurring especially in middle-aged women. To this triad the name Sjögren's syndrome was given, but the variations and increasing complexity of the condition soon became apparent. Holm (1949) reviewing 440 cases of rheumatoid disease stated that "The conception of kerato-conjunctivitis sicca as a disease *sui genesis* (Sjögren) is fundamentally incorrect": but he considered that rheumatoid arthritis was of importance as an aetiological factor.

The term Sjögren's syndrome continued to be applied to any condition in which the classical triad of kerato-conjunctivitis sicca, polyarthritis, and salivary gland enlargement was present, as well as those in which arthritis was absent (approximately 40 per cent. of all cases of kerato-conjunctivitis sicca). Writers, however, remained cautious of associating the condition with rheumatoid arthritis. Coverdale (1948) considered that "Sjögren's syndrome" indicated a general constitutional or systemic disturbance of unknown origin, while Henderson (1950) stated: "I do not feel that polyarthritis is an integral part of the symptom complex. It is my feeling that the arthritis is an incidental finding." Ellman, Weber, and Goodier (1951) remarked that: "rheumatoid arthritis is fairly common among women, and that very few patients with rheumatoid arthritis ever manifest any symptoms resembling Sjögren's disease". They recorded the case history and autopsy findings in a patient who did suffer from rheumatoid arthritis, but in whom the symptoms of xerostoma, salivary gland enlargement, and ocular inflammation preceded the development of the arthritis by several years.

However, Reader, Whyte, and Elmes (1951) confirmed the opinion of Holm (1949) that many patients who suffered from rheumatoid arthritis also had a deficiency of lacrimal secretion, as estimated by Schirmer's test. Other workers have been more inclined to consider kerato-conjunctivitis sicca and its allied pathology as part of the wider concept of rheumatoid disease; this view was expressed by Littler (1951), Gurling (1953), and Morgan (1954).

During the past 3 years, we have treated eighteen patients with severe or moderate kerato-conjunctivitis sicca, fourteen of whom (77·7 per cent.) had rheumatoid arthritis. An additional sixteen patients with milder symptoms and signs, consistent with a condition of conjunctivitis sicca, and also suffering from rheumatoid arthritis, have also been examined and treated. The high percentage of cases associated with polyarthritis is due to the fact that most of the cases were identified at a rheumatic unit. The ophthalmic features, associated lesions, and complications noted in these patients have some points of interest, and are recorded together with some observations on the results of treatment of the ocular lesions.

Incidence

Kerato-conjunctivitis sicca is not the rarity it was once considered to be. It is, indeed, the commonest ocular complication of rheumatoid arthritis. In a recent study of 210 former in-patients of the Rheumatic Diseases Unit, Northern General Hospital,

* Present address: Royal Victoria Infirmary, Newcastle-on-Tyne.

Edinburgh, we found evidence of lesions of the sicca type in thirty patients, an incidence of 14·3 per cent. In comparison with this, there were only seven patients (3·3 per cent.) who showed signs of active or old uveitis. No cases of episcleritis, scleromalacia perforans, or superficial punctate keratitis were identified in this series. These findings accord with those of Holm (1949), who diagnosed kerato-conjunctivitis sicca in 13·4 per cent. of 440 rheumatoid patients, and of Rosenberg (1949) who reported uveitis in 3 to 5 per cent. of cases.

Of the thirty patients with kerato-conjunctivitis sicca in our series, all of whom had had ophthalmic symptoms, six had gross corneal and conjunctival lesions, eight had conjunctival lesions of moderate severity and had only slight corneal changes in addition, and sixteen had conjunctival lesions only, and could be considered to be examples of conjunctivitis sicca.

Sex Ratio

Sjögren (1933) stated that the syndrome occurred most commonly in middle-aged women. Holm (1949) found that female cases predominated, but that in his rheumatoid patients the sex incidence of kerato-conjunctivitis sicca paralleled the sex distribution of the arthritis, being approximately 2·5 females to 1 male. Of the thirty patients in our series, 26 were females, making a ratio of 6·5 females to one male. The sex ratio of the 210 patients studied was only 2·7 females to one male.

Description

Ophthalmic Features.—The classical symptoms and signs of kerato-conjunctivitis sicca are those of conjunctivitis associated with filamentary keratitis and reduction of lacrimal secretion, and the diagnosis can be substantiated by Schirmer's test for lacrimal secretion and the staining reaction with 1 per cent. aqueous Rose-Bengal solution.

In the present series, several ophthalmic features of interest were noted. The ocular symptoms ran a course of remissions and exacerbations, but symptoms were rarely completely absent in severe cases of kerato-conjunctivitis sicca. The waxing and waning of the ophthalmic symptoms in those patients who also had rheumatoid arthritis often occurred independently of any changes in the arthritic condition. Furthermore, the severity of the ocular changes in such patients was not proportional to the severity of the arthritis, some of the most marked examples of kerato-conjunctivitis sicca being encountered in patients with mild or quiescent rheumatoid arthritis.

Although ocular discomfort, photophobia, and mild impairment of vision are well recognized as symptoms of kerato-conjunctivitis sicca, the more serious risks to vision have not been fully appreciated. In the present series, corneal ulceration was noted in three cases. In two instances the ulcers were of the small marginal type which healed without incident. The third patient, however, suffered from bilateral corneal ulceration, and was initially referred to hospital when perforation of a central corneal ulcer necessitated enucleation of the eye. One patient also had a small pannus involving the infero-lateral quadrant of the cornea.

Pathology.—Sjögren (1933) also described the histological features in the lacrimal and salivary glands and in the conjunctiva. In the lacrimal glands the changes consisted of round cell infiltrations, atrophy and destruction of the acini, and replacement fibrosis in the later stages (Fig. 1).

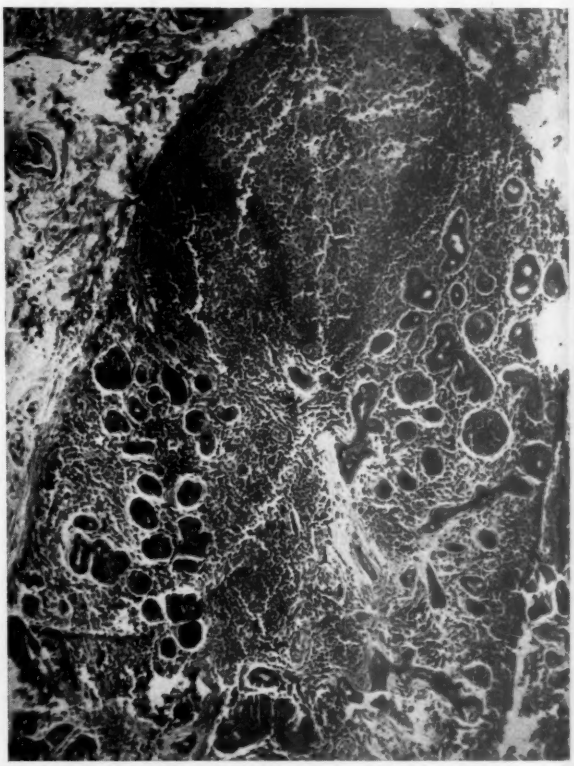


Fig. 1.—Lacrimal gland showing atrophy of acini and extensive round cell infiltration (× 80).

The lesions in the lacrimal glands were considered to be mainly responsible for the dryness of the eyes and the subsequent epithelial changes, but primary degenerative changes in the conjunctival epithelium could also contribute to the developed appearances in kerato-conjunctivitis sicca. The histological changes in the lacrimal glands are similar to those

noted in the salivary glands, but one important difference is that while secretory ducts may be blocked in the salivary glands, this does not occur in the lacrimal glands (Morgan, 1954). This is in keeping with the clinical observation that enlargement of the salivary glands is not uncommon in Sjögren's syndrome, but that enlargement of the lacrimal glands is never seen.

Associated Clinical Features.—The principal conditions, already recorded as associated with kerato-conjunctivitis sicca, and accepted as components of Sjögren's syndrome, are shown in Table I.

TABLE I

CLINICAL FEATURES ALREADY REPORTED IN ASSOCIATION WITH KERATO-CONJUNCTIVITIS SICCA

Rheumatoid polyarthritis
Xerostoma and salivary gland enlargement
Laryngo-pharyngo-rhinitis sicca
Bronchitis and pulmonary atelectasis
Achlorhydria
Vaginitis
Alopecia
Peripheral vascular symptoms
Ichthyosis
Generalized lymphadenopathy
Felty's syndrome
Anaemia
Raised erythrocyte sedimentation rate

It is exceptional for a patient to exhibit most or even many of these features, and usually only polyarthritis and xerostoma are seen. Many of the associated features can be attributed to a deficiency of epithelial glandular secretions and consequent dryness of cutaneous and mucosal surfaces. The co-existence of Sjögren's syndrome and Felty's syndrome, previously noted by Gurling (1953), is further evidence of the common identity of Sjögren's syndrome and rheumatoid disease.

The clinical features in our eighteen cases of severe or moderate kerato-conjunctivitis sicca are shown in Table II. Fourteen of the patients, of whom thirteen were women, had associated rheumatoid polyarthritis. The four patients who had no evidence of arthritis comprised one man and three women. In only two instances had ocular symptoms been noticed before the age of 40 years. The nail changes and otitis externa noted in the present series are worthy of special mention.

TABLE II

CLINICAL FEATURES IN EIGHTEEN CASES OF KERATO-CONJUNCTIVITIS SICCA

Rheumatoid polyarthritis	14
Xerostoma	14
Salivary gland enlargement	6
Laryngo-pharyngo-rhinitis sicca	12
Achlorhydria (five cases examined)	5
Bronchitis and pulmonary atelectasis	5
Alopecia	5
Peripheral vascular symptoms	4
Felty's syndrome	1
Persistent leucopenia	1
Hepatic cirrhosis	1
Marginal corneal ulceration	2
Central corneal ulceration	1
Pannus	1
Trophic nail changes	4
Otitis externa	3

The nail lesions, seen in both fingers and toes, consisted of dry, longitudinally fissured nails (onychorrhexis), stained brownish-yellow. Those most severely involved were rough and irregularly heaped up, due to subungual hyperkeratosis, and such nails grew slowly, gradually separated and sloughed (onycholysis) and then further nail growth commenced from the irregular nail bed. Similar changes in the nails have been recorded in rheumatoid arthritis (Ragan, 1954), but are only rarely encountered, so that their frequency in the present series is especially noteworthy. The most severe nail lesions occurred in a patient who also had arthritis, alopecia totalis, and several other features of the syndrome. This patient received oral cortisone, 100 mg. daily, and normal nail growth was restored (Fig. 2), but there was no improvement in the alopecia.

Fig. 2.—Close-up of left hand of a patient suffering from rheumatoid arthritis, who also exhibited many of the features of Sjögren's syndrome, taken after 2 months' treatment with cortisone, 100 mg. daily. There is a clear line of demarcation between the former discoloured nail and the apparently normal new nail formation.

The occurrence of external otitis in three patients is probably a significant finding in a syndrome where deficiency of epithelial secretions is common. Deficient secretion of cerumen and resultant impairment of normal lubrication of the outer ear passages would predispose to dryness and irritation by dust. The appearances in the affected cases were those of dry, sore ears with small, tender fissures in the

external meatus and helix. The ear wax was dry and powdery, but there was no suppuration or damage to the ear drum. The changes may be described as an otitis externa sicca, comparable to rhinitis sicca.

Treatment

General treatment, by such measures as large doses of vitamins, thyroid extract, and oestrogens, has not proved to be of any value. Local treatments have been directed towards relieving the ocular symptoms. Gifford, Puntenney, and Bellows (1943) employed parasympathomimetic drugs such as pilocarpine nitrate and prostigmine hydrobromide, in an attempt to stimulate lacrimal secretion, and reported success in the treatment of early cases. However, the results have not been impressive in more severe cases, and intestinal cramps limit the dosage of such drugs.

Saline and antibiotic eye drops are not usually helpful because of rapid evaporation. In our experience, artificial tears, which do not evaporate so rapidly, have been of benefit in many mild cases. Methylcellulose drops have been used, and another suitable preparation, suggested by Gifford and others (1943), is:

Gelatin	0·3 g.
Chlorbutal	0·3 g.
Locke's solution	30 ml.

One drop of these "tears" can be instilled into the conjunctiva, three to six times daily.

Deep *x*-ray therapy has been used successfully in reducing the size of the enlarged parotid glands, but no constant improvement has been noted after treatment of the lacrimal glands (Beetham, 1935).

ACTH and cortisone have been administered systemically with conflicting reports of their effect upon lacrimal secretion. In early cases some return of lacrimal secretion has been noted, but side-effects and complications, common to the prolonged administration of high doses of these hormones, have limited the value of this form of treatment. In severe and chronic cases of kerato-conjunctivitis sicca the systemic administration of steroid hormones may relieve the ocular symptoms even though unsuccessful in increasing lacrimal secretion.

Topical administration of cortisone and hydrocortisone has, in our experience, proved to be a safe and useful means of treating mild and moderate cases of kerato-conjunctivitis sicca (Eadie and Thompson, 1955). The eye drops may be prepared in strengths ranging from 0·5 to 2 per cent., and we employed a saline suspension of cortisone acetate diluted in a buffered base. The drops were instilled three to six times daily, according to the severity of the symptoms, and in no instance has any undesirable side-effect been noted as a result of this treatment. Hydrocortisone drops and cortisone eye ointment were used in the treatment of some patients, but did not appear to confer any extra benefit. The local application of these hormones has been shown to be effective solely by virtue of their anti-inflammatory action, as no increase in lacrimal secretion has been noted during their use.

The operation of sealing both lacrimal puncta, in order to conserve diminished secretions, was introduced by Beetham (1935), and has proved to be an effective surgical procedure. Gifford and others (1943) have reported favourably on its value, and we have found it to be helpful in more severe cases of kerato-conjunctivitis sicca that were not adequately controlled by local cortisone therapy. This operation, conveniently done by thermal cauterization of the canaliculus, should not be performed in early or mild cases in whom a remission may be expected, as subsequent improvement in lacrimation would lead to epiphora. In some cases only slight increase in lacrimal secretion, as measured by Schirmer's filter-paper may occur after operation, but in spite of this there may be an appreciable subjective and objective improvement in the eyes. In very severe cases of kerato-conjunctivitis sicca adjuvant therapy with cortisone eye drops or artificial tears may be necessary even after sealing of the lacrimal puncta.

Summary

The clinical features of kerato-conjunctivitis sicca have been described and its occurrence in patients suffering from rheumatoid arthritis has been studied. It is considered to be the most common ocular complication of this disease, having been identified in 14·3 per cent. of a series of 210 patients. Mild cases of kerato-conjunctivitis sicca are especially common, and the minor, recurrent, conjunctival inflammation noted in many patients with rheumatoid arthritis is conjunctivitis sicca, without corneal lesions.

The associated clinical findings have been described in a series of eighteen patients who exhibited the features of Sjögren's syndrome. Changes in the nails and otitis externa sicca have been described. The hazard to vision resulting from corneal ulceration has been emphasized. The treatment of the ocular symptoms has been discussed.

We gratefully acknowledge the invaluable advice and co-operation of Dr. J. J. R. Duthie of the Northern General Hospital, Edinburgh, and of Professor G. I. Scott of the Edinburgh Royal Infirmary. During the period when this work was undertaken the Rheumatic Unit, Northern General Hospital, Edinburgh, was in

receipt of grants from the Nuffield Foundation and Medical Research Council, and one of us (S.E.) received a grant from the W. H. Ross Foundation (Scotland) for the Prevention of Blindness.

The cortisone and ACTH used in the treatment of several of these patients was supplied by the Medical Research Council, to whom we are indebted.

REFERENCES

Beetham, W. P. (1935). *Trans. Amer. ophthal. Soc.*, **33**, 413.
Coverdale, H. (1948). *Brit. J. Ophthal.*, **32**, 669.
Duke-Elder, S. (1930). *Ibid.*, **14**, 61.
Eadie, S., and Thompson, M. (1955). *Ibid.*, **39**, 90.
Ellman, P., Weber, F. Parkes, and Goodier, T. E. W. (1951). *Quart. J. Med.*, n.s. **20**, 33.
Gifford, S. R., Puntenney, I., and Bellows, J. (1943). *Arch. Ophthal. (Chicago)*, **30**, 207.
Gurling, K. J. (1953). *Annals of the Rheumatic Diseases*, **12**, 212.
Henderson, J. W. (1950). *Amer. J. Ophthal.*, **33**, 197.
Holm, S. (1949). *Acta ophthal. (Kbh.)*, Suppl. 33.
Littler, T. R. (1951). *Annals of the Rheumatic Diseases*, **10**, 405.
Morgan, W. S. (1954). *New Engl. J. Med.*, **251**, 5.
Ragan, C. (1953). *In* "Comroe's Arthritis and Allied Conditions", ed. J. L. Hollander, 5th ed., p. 156. Kimpton, London.
Reader, S. R., Whyte, H. M., and Elmes, P. C. (1951). *Annals of the Rheumatic Diseases*, **10**, 288.
Rosenberg, E. F. (1949). *In* "Comroe's Arthritis and Allied Conditions", ed. J. L. Hollander, 4th ed., p. 173. Kimpton, London.
Sjögren, H. (1933). *Acta ophthal. (Kbh.)*, Suppl. 2. (Trans. J. Bruce Hamilton, 1943. Australasian Medical Publishing Co., Sydney.)

La kérato-conjonctivite sèche et l'arthrite rhumatismale

RÉSUMÉ

On décrit les caractères cliniques de la kérato-conjonctivite sèche et on étudie sa fréquence parmi les sujets atteints d'arthrite rhumatismale. On considère que c'est la complication oculaire la plus fréquente, l'ayant identifié dans 14,3% d'une série de 210 malades. Des cas benins de kérato-conjonctivite sèche sont particulièrement répandus et l'inflammation mineure et récurrente des conjonctives, observée chez nombreux rhumatisants est, en réalité, une conjonctivite sèche sans lésions de la cornée.

On décrit les manifestations cliniques secondaires chez 18 malades présentant des traits du syndrome de Sjögren, en particulier les altérations des ongles et l'otite externe sèche. On souligne le danger de l'ulcération de la cornée et on discute le traitement oculaire.

La *kerato-conjunctivitis sicca* y la artritis reumatoide

SUMARIO

Se describen los rasgos clínicos de la kerato-conjunctivitis sicca y se estudia su ocurrencia en sujetos con artritis reumatoide. Se considera que se trata aquí de la complicación ocular la más frecuente, habiéndola identificado en el 14,3% de una serie de 210 enfermos. Casos benignos de *kerato-conjunctivitis sicca* se ven corrientemente y la inflamación menor y recurrente de las conjuntivas observada en numerosos enfermos con artritis reumatoide representa realmente una conjuntivitis seca sin lesiones de la cornea.

Se describen las manifestaciones clínicas secundarias en 18 enfermos presentando rasgos del síndrome de Sjögren, particularmente las alteraciones unguales y la otitis externa seca. Se subraya el peligro de la ulceración de la cornea y se discute el tratamiento ocular.

Ann. rheum. Dis. (1956), **15**, 26.

PULMONARY CHANGES IN DISSEMINATED LUPUS ERYTHEMATOSUS

BY

J. D. AITCHISON AND A. WYNN WILLIAMS

From the Royal Infirmary, Aberdeen, and the Department of Pathology, Aberdeen University

(RECEIVED FOR PUBLICATION DECEMBER 16, 1955)

Pulmonary manifestations in the "diffuse collagen diseases" are said to be commoner than is generally believed and may overshadow the more typical features (Ellman and Cudkowicz, 1954). Over 80 years ago Kaposi (1872) mentioned intercurrent pneumonia in his original account of the visceral lesions of disseminated lupus erythematosus (D.L.E.). Osler (1904) described a case with prolonged consolidation of the lower lobe of the left lung. Subsequent accounts have affirmed the frequency of pleurisy in D.L.E. and, to a lesser degree, of pneumonia.

Until recently, pulmonary changes in D.L.E. have been regarded as the result of secondary bacterial invasion. The possibility of a primary, non-infective involvement of lung was, however, discussed by Klemperer, Pollack, and Baehr (1941), who were impressed by "waxing and waning bronchopneumonia" imperfectly reflected in the *post-mortem* findings. The number of observations on this aspect of the disease is still relatively meagre. In the three cases of the disease described here, the lungs were examined with special care.

Case Reports

Case 1, an unmarried domestic servant, aged 43, had been a healthy woman until August, 1952, when she developed pains in the joints of her hands, severe enough to cause her to be off work for 2 months. During the previous year she had noticed that her fingers became very cold and white in cold weather. In August, 1953, her shoulders and wrists became painful and stiff; later, other limb joints were affected, she felt exhausted, and pyrexia was noted. She was treated with penicillin and sodium salicylate, without apparent improvement. She was admitted to the Royal Infirmary, Aberdeen, in October, 1953.

Examination.—She was an obese, lethargic woman, temperature was 102° F., head hair scanty, skin notably dry and scaly.

Joints.—Movements of the left shoulder, right elbow, knees and ankles were painful and restricted, and the ankles were slightly swollen.

Heart.—The cardiac apex beat could not be felt, there was an apical systolic murmur (Grade III), and the blood pressure was 140/90.

Lungs.—Rales were heard over both lungs, particularly at the bases.

Urine.—A trace of albumin and a few red and white blood cells.

Blood.—Erythrocyte sedimentation rate (Westergren) 135 mm./hr. Wassermann reaction, gonococcal complement-fixation test, Paul Bunnell, and routine agglutination tests were all negative. No cold agglutinins found in the blood. Haemoglobin 8·2 g. per cent.

R.B.C. 2·89 millions per c.mm.
Colour index 0·94.
W.B.C. 4,800 per c.mm.
Differential count essentially normal.
Plasma proteins 7·7 g. per cent., albumin 4·46 g. per cent., globulin 3·24 g. per cent.; blood urea 20 mg. per cent.; serum alkaline phosphatase 5 units.

No abnormality in sternal marrow or cerebrospinal fluid.

Histology.—On 29.10.53 a section of skin from the thigh showed hyperkeratosis, and mild atrophy of the epidermis; there was no evidence of disturbance of collagen.

Radiology.—*X* rays of skull, spine, pelvis, and abdomen revealed no significant abnormality. *X* ray of chest (20.10.53) showed that the transverse diameter of the heart was increased, and the left dome of the diaphragm was somewhat elevated.

Electrocardiogram (26.10.53).—Only sinus tachycardia (Fig. 1*a*, opposite).

Progress.—During the first week in hospital the patient's temperature varied between 100° and 102° F. Thereafter, there was intermittent low grade pyrexia for 3 weeks. The pain in the joints gradually diminished. The erythrocyte sedimentation rate (Westergren) was always above 100 mm./hr.

X ray of the chest (11.11.53) showed heart displaced slightly to left, left dome of diaphragm elevated, linear opacity above left costophrenic angle, consistent with pulmonary infarction, and minimal evidence of a pleural effusion.

On 16.11.53 ACTH was given by intramuscular injection; 25 mg. 6-hrly for 2 days, 25 mg. 8-hrly for 3 days, and 25 mg. twice daily for 7 days. At the end of this course the erythrocyte sedimentation rate had fallen to 46 mm./hr, but a week later it was 116 mm./hr.

On 28.11.53 the patient complained of numbness in the feet and signs of neuritis of both lateral popliteal nerves gradually developed.

On 30.12.53 pyrexia recurred and rales were heard at the left lung base. A further chest *x* ray showed an ill-defined opacity in the same region. During January, 1954, there was pain and stiffness of the shoulders, the erythrocyte sedimentation rate continued above 100 mm./hr., there were occasional small spikes of temperature, the urine contained a small number of red and white cells, and L.E. cells were demonstrated in the peripheral blood.

On 6.2.54 a second course of ACTH was started, with the same dosage as before. On 11.2.54, after 5 days of this treatment, the blood pressure had risen to 205/120 from the usual level of about 140/90, and peripheral oedema developed. ACTH was therefore discontinued immediately, and 2 days later (13.2.54) the blood pressure was 132/70, and the erythrocyte sedimentation rate 73 mm./hr.

Despite the rise in blood pressure, the patient improved in quite a remarkable degree and by 19.2.54 was up and walking about the ward. She was then sent to a small hospital near her home, and a month later, seemed to be further improved, being less easily tired and able to move about more freely, though there was still stiffness and pain in the right shoulder, and the erythrocyte sedimentation rate was 112 mm./hr.

She returned home and was not seen again for nearly 8 months. She had continued to improve gradually throughout the summer and was able to do light tasks in the house until the end of August, 1954. Then she had become breathless, which she attributed to having "caught cold". The breathlessness had become steadily worse until she was distressed lying in bed. She had developed a cough and at times was troubled with wheezing. There had been no haemoptysis or chest pain. She had lost her appetite and lassitude had become severe.

Examination (*1.10.54*).—She was orthopnoeic, the neck veins were filled one inch above the clavicles, as she reclined at 45°, the lips were slightly cyanosed, there was sacral oedema, and the fingers were a bluish-red colour, especially around the nail beds.

Heart.—Blood pressure 130/86, heart sounds quiet, and only a faint systolic murmur could be heard.

Lungs.—At the lung bases, the respiratory murmur was diminished, and the percussion note impaired, and there were abundant rales.

Liver.—The liver edge was felt three finger-breadths below the right costal margin.

Urine.—A moderate number of red blood corpuscles and a small amount of albumin.

Blood.—Haemoglobin 11·2 g. per cent., blood film normal, erythrocyte sedimentation rate 107 mm./hr, plasma proteins 7·87 g. per cent.

Radiology.—*X* ray of chest showed enlargement of cardiac shadow, the contour suggesting that pericardial effusion was present.

Electrocardiogram (Fig. 1*b*).—Marked right axis deviation. In lead aVR, R wave 5 mm. in height,

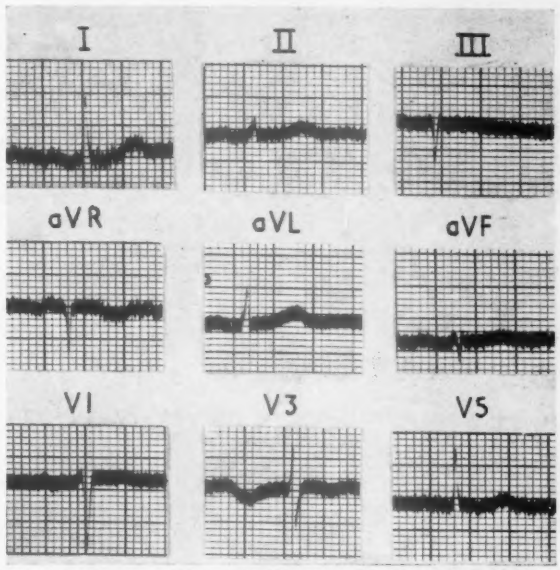


Fig. 1(*a*).—Electrocardiogram in October, 1953, showing no significant abnormality. There is left axis deviation.

and S wave absent; S wave now diminished in lead V1 and present in V5. Although the R waves in the praecordial leads were small, these changes from the tracing of October, 1953, were taken to indicate hypertrophy of the right ventricle and raised the possibility of involvement of the pulmonary vessels by the disease process.

Therapy.—The patient was treated with salt restriction, digitalis, and mercuramide (Neptal). The signs of congestive cardiac failure lessened somewhat but breathlessness remained severe. A purpuric eruption appeared

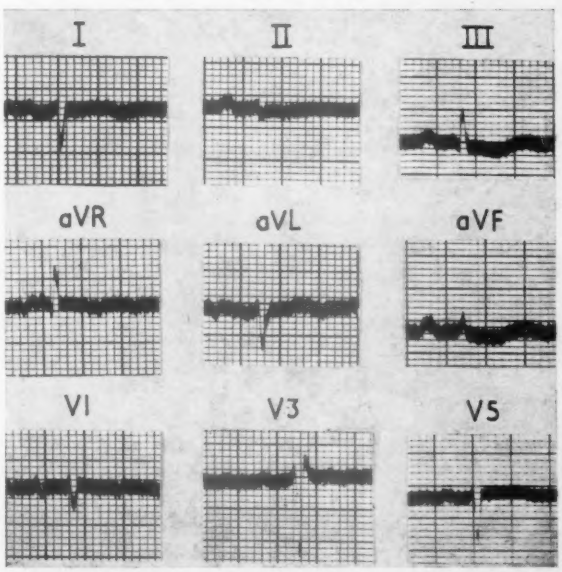


Fig. 1(*b*).—Electrocardiogram in October, 1954, showing development of marked right axis deviation and a tall R-wave in aVR, with evidence of hypertrophy of right ventricle.

on her limbs. She was given chloroquin sulphate (Noviquin) 200 mg. twice daily, but she developed diarrhoea and the drug was discontinued.

Radioscopy (3.11.54) showed evidence of a small pericardial effusion. The respirations became still more rapid and distressed, and on 8.11.54 at 11 a.m. pericardial aspiration was performed and 120 ml. straw-coloured fluid was removed. The procedure was uneventful, but there was no apparent lessening of breathlessness thereafter.

Death.—The patient's condition changed little throughout the day, but at 8 p.m. she became acutely distressed and markedly cyanosed. Despite resuscitative measures, her pulse became imperceptible and she died in a few minutes.

Post-mortem Examination (carried out 16 hours after death).—The body was that of a slightly obese adult female, height 1·6 m. (5 ft. 2 in.), weight 66 kg. (145 lb.). There was marked cyanosis of the head, neck, and hands. Purpuric spots were numerous on the limbs and the skin of the lower limbs was dry and scaly.

There was generalized dilatation of the heart (420 g.), also a healed verrucous endocarditis of the mitral, aortic, and pulmonary valves. In the right ventricle the muscle was markedly hypertrophied and *ante-mortem* thrombus was adherent to the endocardium. Fibrous adhesions and a sero-fibrinous effusion (200 ml.) were present in the pericardial sac. Numerous fibrous adhesions and small serous effusions were found in the pleural sacs. The lungs showed diffuse vascular congestion and oedema, also small scattered foci of collapse. The liver (1,700 g.), spleen (180 g.), and kidneys (combined weight 360 g.) showed chronic venous congestion. A small serous ascites was present. The thyroid (12 g.) was small and partially fibrosed. The right adrenal (3 g.) was small, but the left (7 g.) was normal in size. The brain (1,500 g.) was oedematous.

Histology.

Lungs.—These were congested and oedematous, and contained widely-distributed small foci of collapse, some with interstitial fibrosis (Fig. 2). Fibrinoid change of the intima, media, or whole thickness of the wall was conspicuous in most smaller arteries and arterioles, both pulmonary and bronchial (Figs 3 and 4). In the affected vessels degenerate nuclei were often prominent in the wall (Fig. 5) and invariably there was mural infiltration with large and small mononuclear cells and polymorphonuclear leucocytes, mostly neutrophils. In other small arteries and arterioles, the intima or else the whole wall was thickened by layers of collagen (Fig. 6), while some arteries showed both intimal fibrinoid change and fibrosis of the remainder of the wall. The lumen of the vessels with these various changes was narrowed, often considerably. A rare finding in the small arteries was occlusion of the lumen by *ante-mortem* thrombus, with or without recanalization (Fig. 7). Small haemorrhages were seen in various parts of the lungs, but infarcts were

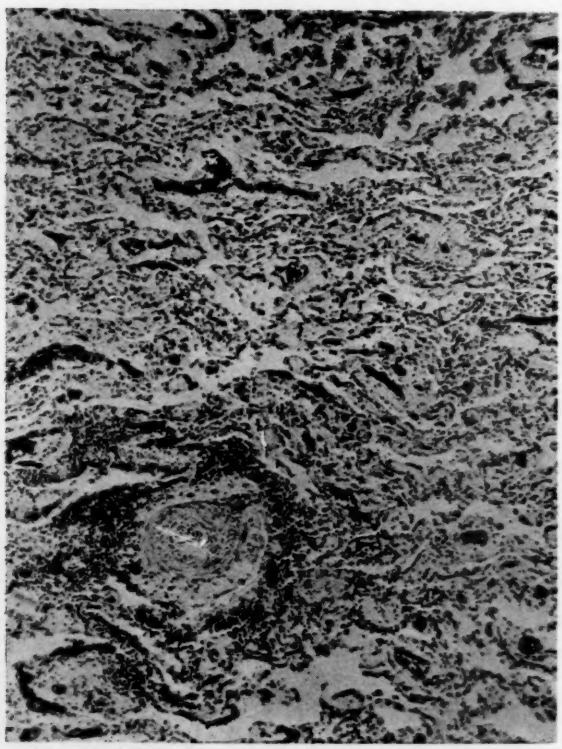


Fig. 2.—Collapsed portion of lung showing interstitial fibrosis and fibrinoid degeneration of an arteriole.
Haematoxylin and eosin (× 60).

Fig. 3.—Fibrinoid degeneration in pulmonary arterioles, also perivascular leucocytosis.
Haematoxylin and eosin (× 60).

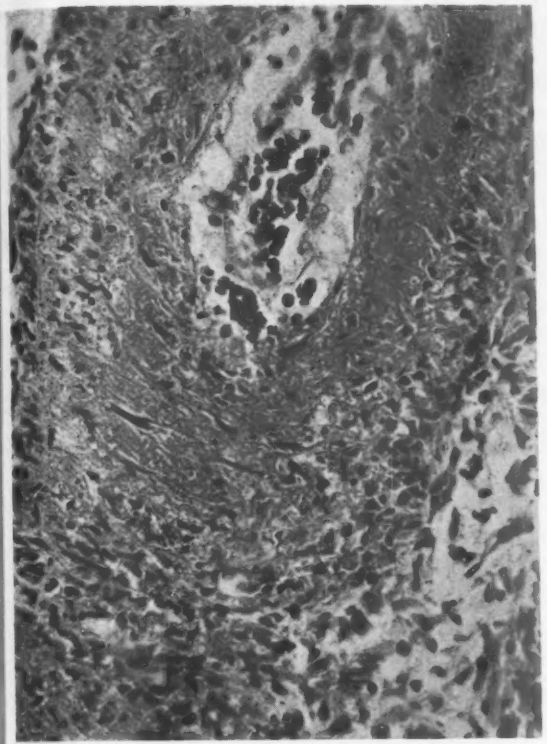


Fig. 4.—Fibrinoid degeneration in pulmonary artery. Haematoxylin and eosin (× 280).

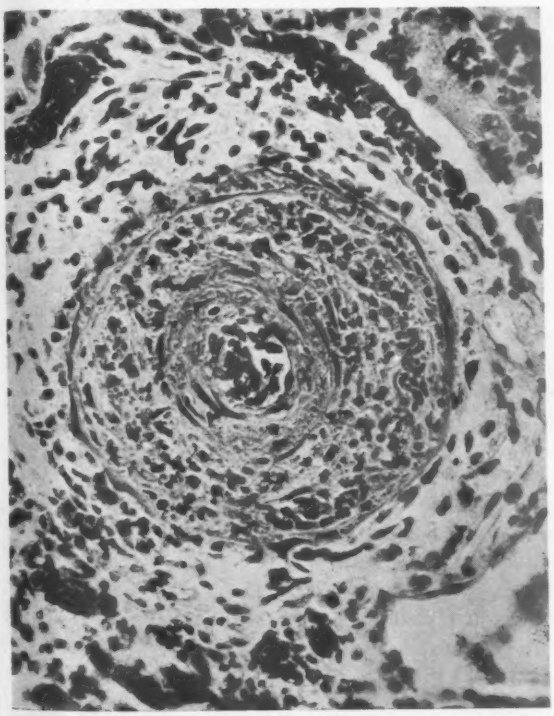


Fig. 5.—Fibrinoid pulmonary artery showing notable intramural nuclear degeneration and leucocytosis, also perivascular leucocytosis. Haematoxylin and eosin (× 280).

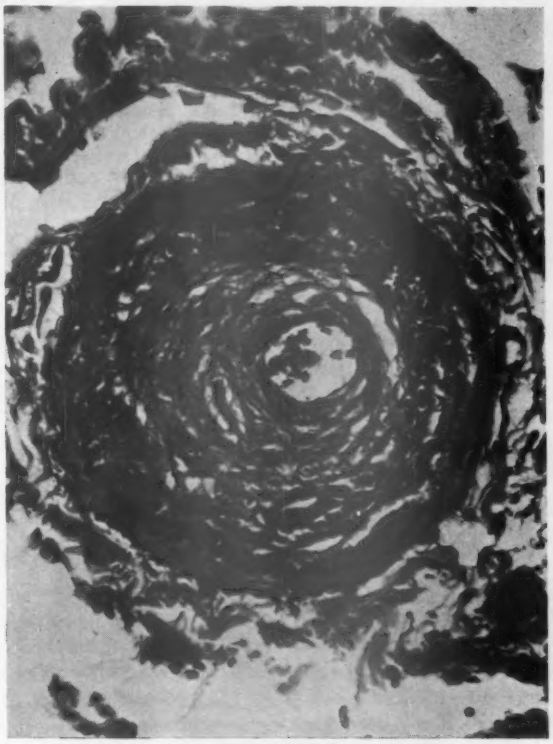


Fig. 6.—Intimal fibrosis in pulmonary artery. Verhoeff-Van Gieson's stain (× 280).

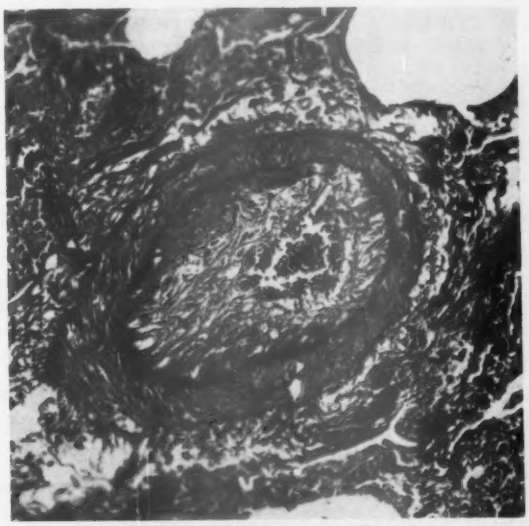


Fig. 7.—Recanalized pulmonary artery. Verhoeff-Van Gieson's stain (× 280).

not present. There was no bronchitis or pneumonia, but collections of small round cells and plasma cells were common around diseased blood vessels.

Heart.—There was evidence of a healed Libman-Sacks disease, affecting particularly the mitral cusps, which were partially calcified, but also the aortic and

pulmonary valves. Slight endocardial fibrosis was present in all the chambers. The myocardium showed some interstitial fibrosis, also a few small fibrinoid foci and a mononuclear cell infiltration, mostly of plasma cells; similar lesions were found in the epicardium. Arterial and arteriolar fibrinoid or fibrous change was found rarely in retroperitoneal connective tissues, pancreas,ovary, stomach, spleen, adrenals, thyroid, skeletal muscles and kidneys. Slight glomerular hyalinosis was present in the latter.

Liver.—Severe centrilobular congestion and mid-zonal fatty change were seen.

Thyroid.—Glandular atrophy and fibrosis were conspicuous.

Kidneys.—Small collections of plasma cells and lymphocytes were observed in the kidneys, and also in the liver, ovaries, skeletal muscles, and skin.

Comment.—The most notable finding was the severity of the pulmonary vascular lesions.

Case 2, a 32-year-old spinster, was admitted to hospital in coma on 26.10.53. Loss of consciousness had been sudden, but for 2 days previously she had had severe frontal headache. A similar attack had occurred a year before, since when she had a permanent hemiplegia. Her health had otherwise been good and there was no obvious clinical manifestation of systemic collagen disease. She died a few hours after admission.

Post-mortem Examination (carried out 12 hours after death).—The main macroscopic findings were an active verrucous endocarditis of the aortic valve; extensive cerebral haemorrhage and also some porencephaly of the right precentral gyrus; pulmonary oedema; old renal and splenic infarcts; fatty liver. The right pleural sac was almost obliterated by dense fibrous adhesions. There were no pleural effusions. The lungs were markedly oedematous. No bronchial or vascular lesions were apparent.

Histology.—The diagnosis of active Libman-Sacks disease was confirmed. Degenerative collagen changes, including fibrinoid lesions, were observed in the endocardium and myocardium, also in the liver. "Wire-loop" lesions were present in the renal glomeruli. Slight fibrinoid changes were found in occasional hepatic and intestinal veins, otherwise no vascular lesions were present. A variable degree of infiltration with large and small mononuclear cells, including plasma cells, was usual where there was degeneration of collagen. There were no skin lesions.

Widespread oedema was seen in the lungs, but no notable vascular changes. A small number of air sacs were lined by hyaline eosinophilic material, partly fibrinoid in character. There was also a minor degree of acute bronchopneumonia.

Comment.—There was severe oedema but no evidence of collagen disease in the lungs.

Case 3, a housewife, aged 33, was admitted to hospital on 1.3.48 with an erythematous rash of the face, malaise, pyrexia, and ulceration of the mouth. She had a history of colitis in 1934, pyelitis in 1936, and puerperal sepsis in 1943. In July, 1947, she had had joint pains of rheumatic type and in August, 1947, a "severe febrile cold". The rash on the face had first appeared in December, 1947.

Examination.—A diagnosis of acute disseminated lupus erythematosus was made. Rhonchi were heard in all areas of the chest.

Treatment.—Penicillin, sulphamezathine, neo-salvarsan, and bisglucol produced no improvement.

Progress.—Pyrexia continued and there was also persistent coughing. On 24.3.48 moist sounds were audible in the lung bases and bronchial breathing in the left base. Signs of congestive cardiac failure were clearly manifest 4 days later and there was no response to treatment.

Death.—The patient died on 30.3.48.

Post-mortem Examination (carried out 20 hours after death).—An extensive scaly, erythematosus eruption was present in the skin of the face and there was superficial ulceration of the skin about the right ear, also of the fingers and toes. Internally, there was an active verrucous endocarditis of the tricuspid and mitral valves and dilatation of all the chambers of the heart. A small sero-fibrinous effusion was present in the pericardial sac and there were large, clear serous effusions in the pleural sacs. Mucus or muco-pus was found in the larger bronchi. In the left lung the lower lobe was collapsed, while in the right lung there were scattered areas of collapse. Small ulcers were seen on the uvula and in the oesophagus. No ascites was present. The liver was enlarged and fatty, but the spleen was normal in size. The kidneys were enlarged and oedematous. There was a paucity of cortical lipoid in the adrenals. Some of the mesenteric lymph nodes were calcified.

Histology.—Degenerative collagen changes were found in the myocardium and endocardium. Fibrinous vegetations were attached to the affected parts of the mitral and tricuspid valves. Evidence of disseminated lupus erythematosus was apparent also in the skin and included fibrinoid thickening of arteries and arterioles. Elsewhere, vascular degenerative changes were seen only in a few small vessels in the myocardium and in a small minority of hepatic veins. In the kidneys, the glomeruli were swollen and showed slight hyaline changes. Collections of mononuclear cells, including plasma cells, were present in tissues presenting degenerative changes. Sections from the lower lobe of the left lung showed considerable collapse, though in sections from the left upper lobe of the right lung there were only occasional collapsed foci. The cause of the collapse was not entirely clear, but muco-pus was present in many of the bronchi, due to chronic bronchitis. Emphysema and some oedema were also present. No notable vascular changes were observed in the lungs.

Comment.—The pulmonary lesion did not present any specific characteristics.

Discussion

It is accepted in most recent published work on D.L.E. that, in some cases of the disease, changes

occur in the lungs which cannot be explained by bacterial infection. There seems little agreement on the nature or incidence of the lesions and even less on their causation.

Klemperer and others (1941) were impressed by the contrast between the "long bouts of waxing and waning migrating bronchopneumonia" and the inconsiderable autopsy findings in the lungs. Such lesions as they found were considered "in no way specific".

Rakov and Taylor (1942) described an example of prolonged consolidation of lung due to "a chronic low grade interstitial pneumonitis". The affected lobes were "atelectatic", but there was no sign of bronchial obstruction.

Foldes (1946) found "chronic interstitial pneumonitis" with massive atelectasis in a case of D.L.E. where death was due to respiratory failure. Teilum (1946) described a "focal allergic pneumonia" in which there was fibrinoid change and histiocytic infiltration of the pulmonary connective tissues. Baggenstoss (1952), although of the opinion that there is no characteristic pulmonary parenchymal lesion, also encountered a case of "chronic interstitial atelectizing pneumonitis", with, in addition, "basophilic mucinous oedema of the alveolar walls". Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954) considered that twenty of their 105 cases of D.L.E. had "lupus pneumonitis". Seven of the twenty came to autopsy and showed the following microscopic changes: hyaline alveolar membranes, focal necrosis of alveolar walls with capillary thrombi, areas of organizing interstitial pneumonia and haemorrhage, and "metaplasia of the bronchiolar epithelium".

There is some evidence that vascular lesions occur in the lungs in D.L.E. Over 20 years ago Baehr, Klemperer, and Schifrin (1935) reported an unusual degree of involvement of the vessels of the lesser circulation in four of a series of 23 autopsied cases of D.L.E. There was notable enlargement of the right heart in all four cases and three died in congestive cardiac failure. However, Klemperer and others (1941) found lesions of systemic implication in the small pulmonary arteries of only a single case among twenty autopsied. Wood (1952), in an account of pulmonary hypertension, included D.L.E. as a cause. Ellman and Cudkowicz (1954), in a review of the pulmonary lesions in the diffuse collagen diseases, have put forward the view that "the lung changes in this disease group may represent the effects of progressive pulmonary ischaemia resulting from the loss of a bronchial arterial blood supply".

Tumulty and Harvey (1949) described infiltration of the lungs in three autopsied cases of D.L.E. as "typical of the changes seen in rheumatic fever, periarteritis nodosa, and sulphonamide hypersensitivity".

There is a notable similarity between the description by Thorell (1952) of the radiological findings in cases of D.L.E. with pulmonary and pleural involvement and those met in pulmonary infarction (Macleod and Grant, 1954). Thorell described small, bilateral pleural effusions and pleural thickenings, often accompanied by parenchymal changes, commonly subpleural and basal in situation.

Only in our Case 1 could we identify morphological changes of distinctive character in the lungs. The severe degenerative and fibrotic pulmonary vascular changes were clearly similar to those found in other parts of the body and seemed to be the result of the disease process affecting the vessel walls. The obstruction to the blood flow to the lungs, caused in this way, led to hypertrophy of the right ventricle, detected by electrocardiogram and confirmed at autopsy. Physical signs in the lungs were ill-defined and difficult to interpret. Breathlessness, however, was severe and from time to time there was evidence, especially radiological, of pulmonary infarction. It seems probable that, although the fully developed picture of cor pulmonale occurs in a minority of cases of D.L.E., the pulmonary vessels may be involved more often than has been realized. It may be that some of the ill-defined lesions which are found in the lungs clinically, radiologically, and at *post-mortem*, are the result of occlusive changes in the lung vessels.

The reason for the peculiar concentration of vascular lesions in the lungs of Case 1 and the absence of such changes in our other two cases of D.L.E. is not known.

Summary

A description is given of the changes found in the lungs of three female patients, aged 43, 32 and 33 years, who presented the essential manifestations of disseminated lupus erythematosus.

In the oldest patient there were widespread degenerative and fibrous changes in the smaller pulmonary arteries and arterioles. In the other two patients there were no specific lung lesions.

Brief reference is made to the literature on the subject of lung changes in disseminated lupus erythematosus.

We are grateful to Dr. R. J. Duthie and Prof. J. S. Young for permission to publish these cases and for helpful advice and criticism.

REFERENCES

Baehr, G., Klemperer, P., and Schifrin, A. (1935). *Trans. Ass. Amer. Phys.*, **50**, 139.
Baggenstoss, A. H. (1952). *Proc. Mayo Clin.*, **27**, 412.
Ellman, P., and Cudkowicz, L. (1954). *Thorax*, **9**, 46.
Foldes, J. (1946). *Amer. J. clin. Path.*, **16**, 160.
Harvey, A. McG., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. (1954). *Medicine (Baltimore)*, **33**, 291.
Kaposi, M. K. (1872). *Arch. Derm. Syph. (Wien)*, **4**, 36.
Klemperer, P., Pollack, A. D., and Baehr, G. (1941). *Arch. Path. (Chicago)*, **32**, 569.
Macleod, J. G., and Grant, I. W. B. (1954). *Thorax*, **9**, 71.
Osler, W. (1904). *Amer. J. med. Sci.*, **127**, 1.
Rakov, H. L., and Taylor, J. S. (1942). *Arch. intern. Med.*, **70**, 88.
Teilum, G. (1946). *Acta med. scand.*, **123**, 126.
Thorell, I. (1952). *Acta radiol. (Stockh.)*, **37**, 8.
Tumulty, P. A., and Harvey, A. McG. (1949). *Bull. Johns Hopk. Hosp.*, **85**, 47.
Wood, P. (1952). *Brit. med. Bull.*, **8**, 348.

Altérations pulmonaires dans le lupus érythémateux disséminé

RÉSUMÉ

On décrit les altérations pulmonaires chez trois femmes de 43, 32 et 33 ans présentant les manifestations essentielles du lupus érythémateux disséminé.

Chez la plus vieille des trois malades il y eut des lésions fibreuses et de dégénérescence étendues dans les artères pulmonaires secondaires et dans les artérioles. Chez les deux autres on ne trouva pas de lésions pulmonaires spécifiques.

On mentionne brèvement la littérature sur les lésions pulmonaires dans le lupus érythémateux disséminé.

Alteraciones pulmonares en el lupus eritematoso diseminado

SUMARIO

Se describen las alteraciones pulmonares en tres enfermas de 43, 32 y 33 años presentando manifestaciones esenciales de lupus eritematoso diseminado.

En la mujer de 43 encontráronse extensas lesiones fibrosas y degenerativas en las arterias pulmonares secundarias y en las arteriolas. En las demás no hubo lesiones pulmonares especificas.

Se menciona brevemente la literatura sobre lesiones pulmonares en el lupus eritematoso diseminado.

Ann. rheum. Dis. (1956), **15**, 33.

MODERN TRENDS IN ACUTE RHEUMATISM

BY

S. LEFF

(RECEIVED FOR PUBLICATION JUNE 13, 1955)

The last few years have witnessed a marked decline in the incidence of acute rheumatic infection in childhood, but it "is still a dangerous menace demanding the continued attention of paediatricians, public health officers, and laboratory workers" (Annotation, 1955). The serious nature of the disease was revealed in a follow-up of children in the United States: after 10 years approximately one in three had died, and after 20 years more than half (Ash, 1948); in general, a rheumatic child has but a fifty-fifty chance of surviving to the age of 40 years (Wilson and Lubschez, 1948). Rheumatic heart disease is probably responsible for the deaths of one in ten of all heart sufferers and for practically all the deaths from heart disease of persons below the age of 40 years; in the under 40s it takes second place only to tuberculosis.

Incidence and Trends

It is difficult to estimate the incidence of rheumatism of childhood: perhaps no disease is so unpredictable—its appearance often varies in successive attacks, and the extent of damage to the heart is often unrelated to the severity of the attack. The acute form is easily recognized, but the insidious (sub-acute) form with vague growing pains and no obvious involvement of the joints may easily be missed; often the only sign that a child has suffered from rheumatism is the finding of a damaged heart. Nevertheless, it is possible to estimate the incidence of this disorder from a study of the mortality and attack-rates of acute rheumatic fever and of the numbers suffering from rheumatic heart disease.

Mortality.—The Registrar-General's returns of mortality from rheumatic fever and heart disease in persons under 15 years of age for England and Wales give some indication of the incidence of acute rheumatism (Table I). Until 1947 these returns were almost the only reliable sources of information.

Mortality declined steadily from 1938 to 1942 with a probable simultaneous fall in incidence (Glover, 1943; Gale, 1945). There was a sharp rise in mortality in 1943 followed by a fall to a new low point in 1946. In 1947 and again in 1948 slight rises occurred, followed by substantial decline in 1950 (17 per cent. for males and 20·7 per cent. for females); the preponderance of female over male deaths was less in 1950 than ever before. There was a further and greater substantial decline in 1951, when the mortality was just less than one-half of that in 1946, the first post-war year. Further reductions in the following years were greater for females, with the result that in 1953 the mortality for females was only very slightly higher than for males.

Incidence of Heart Damage.—In a disease with a low mortality it is impossible to judge accurately the incidence from the number of deaths alone. In a recent observation period of one year, there were only six deaths among 497 patients under the age of 16 (M.R.C. and A.H.A., 1955), but even a knowledge of the number of cases of rheumatic fever or acute rheumatism is not enough, because the main danger is from damaged hearts, which often develop after few or no symptoms as in the sub-acute forms. Another indication of the extent of this disorder can

TABLE I

DEATHS FROM RHEUMATIC FEVER (CLASSIFIED BY 6A REVISION, ENGLAND AND WALES)

Year ..	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
Males ..	509	448	380	406	446	416	360	350	363	312	259	164	144	143
Females ..	742	565	513	623	556	521	415	427	449	391	310	214	184	167
Total ..	1,251	1,013	893	1,029	1,002	937	775	777	812	703	569	378	328	310

therefore be obtained from estimates of the number of damaged hearts caused by rheumatism.

In the United States, about 30,000 people under the age of 25 years develop rheumatic fever or chorea every year; and 600,000 under 50 years of age have rheumatic heart disease (Hill and others, 1949). The rejection from military service of four in ten young men with heart disease in San Francisco, and of seven in ten in Chicago, was due to rheumatic heart damage (Griffith, 1948).

Parkinson (1945) quoted Dr. Stocks's estimate that in Great Britain there were at least 300,000 persons of both sexes with heart disease, the majority rheumatic in origin. It appeared that this estimate was too high, but in a study of returns of mass-radiography over a period of 3 years the incidence of rheumatic heart disease was found to be 4 per 1,000 (Kerley, 1949), and was in fact probably higher, since the *x* ray detected only considerable alterations in the shape or size of the heart. Parkinson urged that a central national committee should be set up to organize and extend existing special facilities, such as supervisory clinics and long-stay hospital schools, thus providing greater opportunities for much needed research into causation and prevention.

Early in 1946, at the request of the Minister of Health, the President of the Comitia of the Royal College of Physicians appointed a special committee "To consider the prevention and management of rheumatic heart disease". This committee recommended that acute rheumatism, including valvular disease of the heart, in school children up to 16 years of age should be made compulsorily notifiable. In October, 1947, this was put into operation in Bristol and Sheffield, and also in a mixed urban and rural area, where there were good facilities for the diagnosis and treatment of rheumatic fever. The results are shown in Table II. It was hoped that the relative incidence in the different areas would give some indication of the importance of genetic and social factors in the evolution of the disorder.

In 1948 the number of notifications already reflected the great decline in incidence compared with 20 years before. In the first year, after clinical examination and in some cases a period of observation, only just over 60 per cent. were accepted as suffering from acute rheumatism in an active stage; nearly 20 per cent. of notified cases had quiescent heart disease, and 10 per cent. heart disease of non-rheumatic origin. The incidence was thus less than 1 per 1,000 of the child population, and in some areas less than 0·5 per 1,000. Similar evidence of a decline in incidence was suggested by using data from a children's supervisory rheumatism clinic at Walthamstow (Sheldon, 1948).

In 1950, on the recommendation of the Rheumatic Fever Committee of the Royal College of Physicians, two more towns and one rural area were added for notifications, raising the number of the child population at risk from just over 300,000 to over 500,000 (Table II). The notification rate per 1,000 children per annum for 1950 was 0·45 compared with 0·35 in 1949 and 0·55 in 1948; 0·27 per 1,000 had acute rheumatism with active rheumatic heart disease.

It is estimated that, if these figures were applied to the country as a whole, between 4,000 and 5,000 new cases of acute rheumatism occurred in children of school age every year; a review of the evidence indicated that the post-war attack-rates were only one-third or one-quarter as great as the pre-war figures (Conybeare, 1951). The decline has not been uniform; in 1951, the rate in some areas was less than one-half that in 1950, but there was little change in the totals for 1952/53, when there were increases in the two large towns and there were reductions in the rural areas.

Causes for the Decline in Incidence.—Knowledge

TABLE II

NOTIFICATION OF ACUTE RHEUMATISM
(1948-50, 4 TOWNS AND 2 COUNTIES; 1950-53, 6 TOWNS AND 3 COUNTIES)

Year	Estimated Child Population, 0-14 yrs (approx.)	Total Notified Cases	Classification of Notified Cases			
			Acute Rheumatism	Chronic Rheumatic Heart Disease	No Rheumatism	Not Classified
1948	309,000	271	170	48	39	14
1949	313,000	134	110	3	20	1
1950	319,000	173	141	4	20	8
1951	510,000	162	130	8	23	1
1952	510,000	161	133	6	22	—
1953	510,000	184	149	1	31	3

of the causes of this decline in incidence can help to guide future policy in prevention and treatment. Three main causes have been suggested: a change in the relationship between man and the haemolytic streptococcus, better methods and facilities for prevention and treatment, and improvements in the social environment with the decline in the general extent of poverty.

(1) *Haemolytic Streptococcus and Acute Rheumatism.*—There is strong evidence of the association of the haemolytic streptococcus with acute rheumatism. A haemolytic streptococcus infection often precedes the attack by 2 to 4 weeks, and it has been estimated that rheumatic sequelae complicate 1-2 per cent. of streptococcal upper respiratory infections (Leader, 1953). Several epidemics of streptococcal pharyngitis and scarlet fever occurred during World War II, followed by a high incidence of rheumatic fever or relapses, and a study of the sickness records of the R.A.F. showed that morbidity from rheumatic fever and scarlet fever were closely related in young adults (Macdonald, 1950). Except for the year 1942 the rise and fall of the figures for deaths from rheumatic fever have been paralleled by the number of notified cases of scarlet fever.

Rheumatic subjects have a much higher carrier rate of Group A streptococci in their throats (50·5 per cent. as compared with 12·5 per cent. of normal), and there is often a reappearance or an increase in the numbers of haemolytic streptococci in the throats of individual cases of rheumatic fever which relapse. Haemolytic streptococci have been grown from rheumatic fever necropsies from the tonsils, cervical and mediastinal glands, and heart valves (Collis, 1931; Green, 1939, 1942).

Rheumatic subjects display a considerably higher skin sensitivity to streptococcal extracts (endotoxins) than normal subjects, and it is possible to measure the antibody titre for streptococcal haemolysin in human serum (Todd and others, 1939). This reaction is specific to the streptococcus and is not an expression of the rheumatic individual's general hyperactivity of an immune response (Miller and others, 1953; Kuhns and McCarty, 1954). About 80 per cent. of rheumatic fever cases show a rise of streptolysin -O titre which reaches its maximum in 3 to 4 weeks (Mote and Jones, 1941; Green, 1941).

It has been suggested that the decline in the incidence of rheumatic fever and in the mortality from scarlet fever is due either to the fact that man is more immune, or to the fact that the streptococcus is less virulent (Glover, 1946).

It must be remembered that, although streptococcal infection is commonly associated with rheumatic fever, it is not an exclusive factor, and in one series it accompanied only thirteen out of 42 cases; the rheumatic fever followed many varied infections of Eastern desert life, such as malaria, dysentery, and sandfly fever (Copeman, 1944).

(2) *Prevention and Treatment.*—Chemoprophylaxis is now used in an effort to avoid rheumatic fever sequelae by streptococcal infections during the acute phase, both in the primary attack and in relapses, and by sterilizing the upper respiratory passages of carriers.

Sulphonamides were first used but resistant strains appeared and toxic symptoms occasionally developed. Oral penicillin, 200,000 units three times daily on an empty stomach was then given as a prophylactic (Bywaters, 1954), but it had to be given for a long period, and it did not seem to affect rheumatic fever recurrences, although it markedly reduced the number of occasions streptococci were isolated from the throat (Gale and others, 1952). The Chief Medical Officer of the Ministry of Health (1953) commented on its use as follows:

> It seems, in fact, unlikely that the more or less continuous oral administration of penicillin is a really practicable means of preventing rheumatic heart disease.

More recently, better results appear to have been given by intramuscular injection of long-acting penicillins (Benzethacil or Bicillin, N,N^1-dibenzykethylenediamine dipenicillin G) monthly with no significant toxicity (Diehl and others, 1954; Stollerman and Rusoff, 1952). Group A streptococci were eliminated from the throats of carriers and new infections were almost completely prevented (Perry and Gillespie, 1954). Aureomycin has also been used with good results in a small group of cases (McVay and Sprunt, 1953).

Recently, the American Heart Association's committee published its recommendations on the prevention of rheumatic fever (American Heart Association, 1953). For treating streptococcal infections, intramuscular procaine penicillin is suggested, given early and continued until the organisms are eradicated from the throat (Wannamaker and others, 1951). For preventing streptococcal infections, sulphadiazine is suggested because of its relative low cost in prolonged administration; the risk of developing resistant organisms is much less in the rheumatic patient treated at home compared with the mass prophylaxis in closed communities under Service conditions (Finland, 1951).

Chemoprophylaxis is clearly a very big undertaking; it should include all those under the age of 18 who have had rheumatic fever or chorea, and also all those over 18 who have had an attack within 5 years (Bland and Jones, 1951), and as it could not control large reservoirs of infection (Kohn and others, 1953), either larger doses would have to be given or the tonsils of all those at risk would have to be examined periodically. Even if the evidence for the efficacy of chemoprophylaxis were much stronger, the problems of the prevention of the first attack of rheumatic fever and of the mild symptomless case would still have to be faced.

Chemoprophylaxis has been in use for too short a period to have played a significant part in the decline in incidence.

Nor has treatment taken an important role in the decline in incidence. When cortisone was introduced, it was thought that a powerful new weapon had been found in the struggle against acute rheumatism. But the results proved disappointing. Many reports revealed that while cortisone and ACTH had a suppressive action, they had little effect in preventing the progress of valvular

and heart disease (Kuttner and others, 1952; Sheinkoff and others, 1952). Better results were obtained by giving cortisone early before overt clinical damage had occurred (Wilson, 1953), and ACTH given by continuous intravenous drip, while not improving results, cut down drug costs to only one-tenth of that required in intramuscular therapy (Griffith and others, 1952).

Controlled experiments have revealed that there is very little to choose between salicylates and cortisone (Illingworth and others, 1954). Recently, three randomly controlled groups covering 497 patients (240 in Great Britain and 257 in the United States) were treated with ACTH, cortisone, and aspirin, and at the end of one year there was no significant difference between the three groups in the status of the heart (M.R.C. and A.H.A., 1955); none of the three drugs produced uniform termination of the disease, and with each of them some patients developed fresh manifestations during treatment. The hormones controlled certain acute manifestations more promptly, but the symptoms had a greater tendency to reappear for a limited period after cessation of treatment. The results of treatment were measured against such separate manifestations as temperature, pulse-rate during sleep, erythrocyte sedimentation rate, joint involvement, chorea, erythema marginatum, nodules, and the status of the heart—its size, atrioventricular conduction time, murmurs, congestive failure, and pericarditis.

A survey over a longer period may show that the hormone-treated group has an advantage, but this seems unlikely to be spectacular. It has even been suggested that the action of salicylates and cortisone is similar (Leader, 1951a; Annotation, 1955), though it seems improbable that the salicylates produce their action by increasing adrenocortical activity.

Other drugs such as Butazolidin have met with no greater success (Fleming and Will, 1953), and although better results might be obtained by combining Butazolidin with penicillin, caution must be exercised because of the risk of liver damage (Hockerts, 1953).

(3) *Social Measures.*—A good rheumatism scheme can play an important part in reducing the incidence of rheumatic fever and its relapses. Such a scheme should include proper centres for educating the public, detecting cases early, and supervising patients when they come out of hospital, by arranging for additional foods and clothing, special holiday facilities, and rehousing. For damaged hearts special facilities should be provided, such as prolonged rest in hospital schools together with continuation of treatment and schooling in special day and convalescent schools.

There has been no marked expansion in the services in the past few years to conform to such a scheme. In 1947 a special unit of 100 beds for the study and care of juvenile rheumatism was attached to the Canadian Red Cross Memorial Hospital, Taplow, with a plan to expand to 200 beds. Other centres have been established at London, Sheffield, Newcastle, and Cardiff, but they cannot yet have played a significant role in the general decline of rheumatic fever in the country as a whole.

Family studies (Gray and others, 1952; Stevenson and Cheeseman, 1953), including pedigrees of rheumatic families (Pickles, 1943; Beers, 1949), and records of identical and non-identical twins (Kaufmann and Scheerer, 1938; Perry, 1940), have suggested that heredity is involved, and a recent long-term study appears to have confirmed this (Wilson and Schweitzer, 1954), but no study has been able to overcome completely the usual difficulties of using diagnoses universally accepted, of unreliable histories, and of selecting families for the controls equivalent to those which have a rheumatic subject.

Other studies, however, have been even less definite. One confirmed the well-known relative immunity of blue-eyed children based on some genetic factor, but found no evidence that some families are more prone to develop rheumatic fever than others (Hewitt and Stewart, 1952). Another suggested that the mode of transmission of susceptibility is best left an open question; no significant difference was found between the families with an affected parent and those with normal parents (Uchida, 1953). Another suggested that the incomplete manifestation of the disease makes it difficult to determine the exact mode of inheritance, although it is possible to exclude both the hypothesis of a single autosomal completely dominant gene and that of complete sex-linkage (Stevenson and Cheeseman, 1953).

Even where heredity is considered to play a part, it is admitted that the more important factors are probably exposure to streptococcal infection and conditions of poverty. In any case the recent decline in the incidence of rheumatic fever could not possibly have been due to changes in genetic factors, because insufficient time has elapsed for them to have developed.

Many workers have emphasized the significance of social conditions in the evolution of rheumatic fever (Ryle, 1946; Perry, 1944), but recently with the decline in incidence there has been a tendency to minimize their importance, because the social differences are no longer so marked (Leader, 1951b). It has recently been suggested that there is no evidence that acute rheumatism is associated either with bad housing conditions or with poverty *per se*, and that the size of the household and the ages of the children included in it are more important (Hewitt and Stewart, 1952).

Before the war the rheumatic heart death rate was strongly associated with industrial and town life, and, above all, with poverty (Morris and Titmuss, 1942). Fig. 1 (opposite) illustrates the mortality rates in children of school age (5-15 yrs) in county boroughs, urban districts, and rural districts, in England and Wales, compared with those in the comparatively rural and well-to-do S.W. England and the predominantly industrial and poverty-stricken S. Wales in the years 1929-33.

It was perhaps even more sensitive to social conditions than infant mortality or the phthisis death rate in young women, and it responded to even short changes in such conditions, as measured by the level of unemployment (Morris and Titmuss, 1944).

A study of the county boroughs of England and Wales classified in ten groups (A to J) according to their experience of unemployment between 1927 and 1938 showed

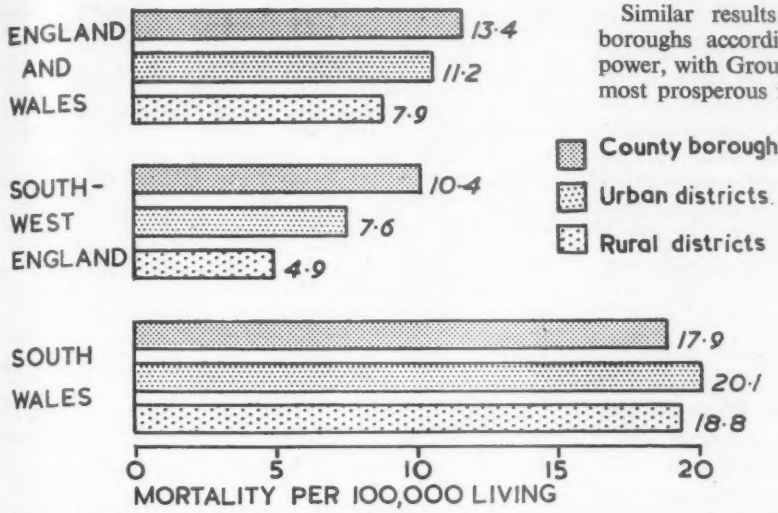


Fig. 1.—Mortality from heart disease per 100,000 living, in children aged 5 to 15 yrs, both sexes combined, in England and Wales, S.W. England, and S. Wales, by county boroughs, urban districts, and rural districts, in 1929-33.

a marked difference in mortality from rheumatic heart disease in Group A (towns which suffered most unemployment) and in Group J (towns with least unemployment). Although there has been a closing of the gap between these two groups as a result of the post-war improvement in social conditions and the decline in mortality, a marked difference still exists (Fig. 2).

Similar results are obtained by grouping county boroughs according to income levels and purchasing power, with Group 1 as the poorest and Group 4 as the most prosperous in 1949-50 (Fig. 3).

Even in discussing other factors in the causation of the decline in incidence, due regard has to be given to such changes in the social environment such as the decrease in poverty caused by abundant employment during wartime, the greatly increased provision of milk for all children and of solid meals for school children, the more balanced diet for everyone due to rationing and the national flour and bread, and the long "changes of air" due to evacuation which at the most susceptible ages tended to decrease the effect of urbanization (Glover, 1946). A recent study links the role of the streptococcus with that of the social environment by demonstrating that the carrier rate of the streptococcus varies with the rate of tonsillectomy, the amount of the rental, and the incidence of rheumatic fever (Holmes and Rubbo, 1953).

Clearly, of all the factors responsible for the decline in the incidence of acute rheumatism in childhood, the improvement in the social conditions

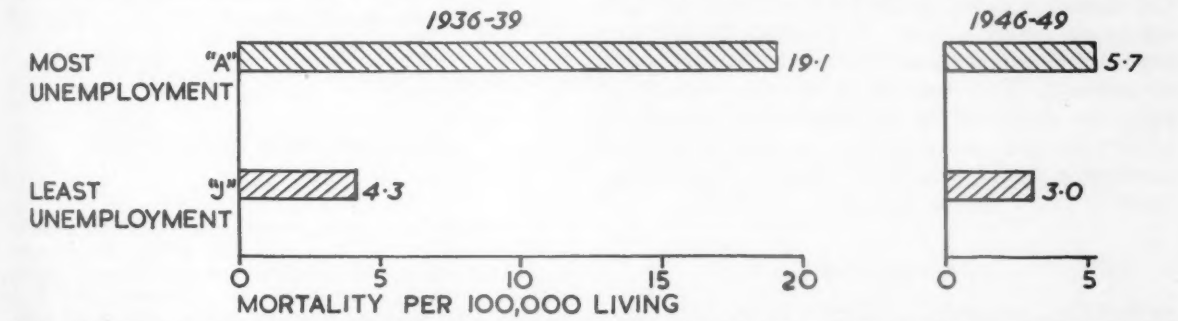


Fig. 2.—Mortality from heart disease per 100,000 living, in children aged 5 to 15 yrs, both sexes combined, in areas of least unemployment in S. Wales (J) and most unemployment in England and Wales (A), comparing the periods 1936-39, and 1946-49.

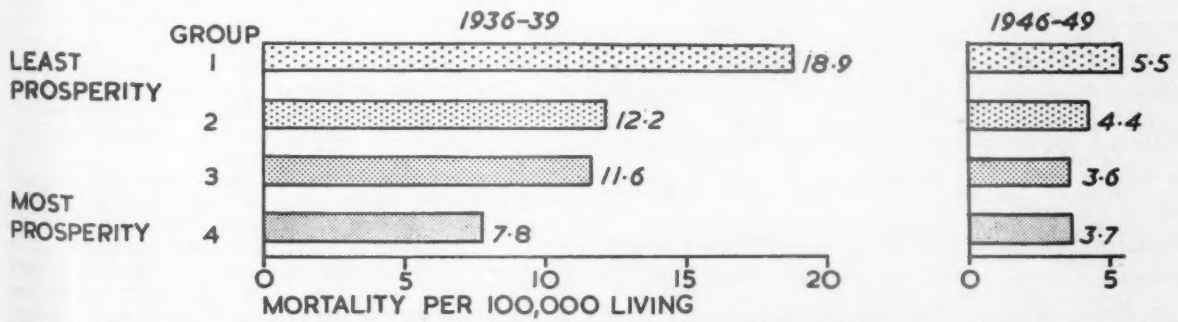


Fig. 3.—Mortality from heart disease per 100,000 living, in children aged 5 to 15 yrs, both sexes combined, in county boroughs of four grades of prosperity (1-4), comparing the periods 1936-39, and 1946-49.

stands out as the most important. This finding serves as a guide for the future in the struggle against this disorder. For example, Fig. 3 shows that where the purchasing power and income levels are highest, the mortality from rheumatic heart disease is reduced by about 50 per cent. Essentials in improved social conditions are better housing, meals at school, protective clothing, and adequate convalescent and rest-home facilities. In addition, better facilities for prevention and treatment will play an important part.

Summary

Deaths from rheumatic fever in England and Wales declined from 1,251 in 1940 to 310 in 1953; annual post-war figures, estimated at between 4,000 and 5,000 new cases in school children, were between a third and a quarter of pre-war figures.

Streptococcal infection is commonly associated with rheumatic fever, but is not an exclusive factor. Good results have been obtained by some methods of chemoprophylaxis, but these have been in use for too short a period to have been a significant factor. Treatment with cortisone and Butazolidin has proved disappointing. There has been no large-scale expansion of special rheumatism centres.

Heredity may play a part, but insufficient time has elapsed for changes in genetic factors to be a significant cause. More important factors are exposure to streptococcal infections and conditions of poverty. The importance of environment is shown in studies of the incidence of the disease in towns grouped according to income levels and purchasing power, which still show marked differences, despite a general decline in mortality.

REFERENCES

American Heart Association (1953). *Lancet*, **1**, 285.
Annotation (1955). *Brit. med. J.*, **1**, 589.
Ash, R. (1948). *Amer. J. Dis. Child.*, **76**, 46.
Beers, C. V. (1949). *Hereditas* (*Lund*), Suppl. vol.: "Proc. 8 int. Congr. Genetics, 1948", p. 534.
Bland, E. F., and Jones, T. D. (1951). *Circulation*, **4**, 836.
Bywaters, E. G. L. (1954). *Courrier* (*Paris*), **4**, 357.
Collis, W. R. F. (1931). *Lancet*, **1**, 1341.
Conybeare, E. T. (1951). *J. roy. San. Inst.*, **71**, 300.
Copeman, W. S. C. (1944). *Annals of the Rheumatic Diseases*, **4**, 11.
Diehl, A. M., Hamilton, T. R., Keeling, I. C., and May, J. S. (1954). *J. Amer. med. Ass.*, **155**, 1466.
Finland, M. (1951). *Bull. N.Y. Acad. Med.*, **27**, 199.
Fleming, J., and Will, G. (1953). *Annals of the Rheumatic Diseases*, **12**, 95.
Gale, A. H. (1945). *Arch. Dis. Childh.*, **20**, 2.
——, Gillespie, W. A., and Perry, C. B. (1952). *Lancet*, **2**, 61.
Glover, J. A. (1943). *Lancet*, **2**, 51.
—— (1946). *Monthly Bull. Minist. Hlth* (*Lond.*), **5**, 222.
Gray, F. G., Quinn, R. W., and Quinn, J. P. (1952). *Amer. J. Med.*, **13**, 400.
Green, C. A. (1939). *Annals of the Rheumatic Diseases*, **1**, 86.
—— (1941). *J. Path. Bact.*, **53**, 223.
—— (1942). *Annals of the Rheumatic Diseases*, **3**, 4.
Griffith, G. C. (1948). *Amer. J. Publ. Hlth*, **38**, 682.
—— and others (1952). ? ? ? ?
Hewitt, D., and Stewart, A. (1952). *Brit. J. soc. Med.*, **6**, 161.
Hill, L. F., Hubbard, J. P., Harris, T. N., Jackson, R. L., and Wheatley, G. M. (1949). *Pediatrics* (Panel Discussion on Rheumatic Fever), **3**, 680.
Hockerts, T. (1953). *Dtsch. med. Wschr.*, **78**, 669.
Holmes, M. C., and Rubbo, S. D. (1953). *J. Hyg.*, **51**, 450.
Illingworth, R. S., Burke, J., Doxiadis, S. A., Lorber, J., Philpott, M. G., and Stone, D. G. H. (1954). *Quart. J. Med.*, **23**, 177.
Kaufmann, O., and Scheerer, E. (1938). *Z. mensch. Venerb. KonstLehre*, **21**, 687.
Kerley, P. (1949). *Proc. roy. Soc. Med.*, **42**, 1042.
Kohn, K. H., Milzer, A., and MacLean, H. (1953). *J. Amer. med. Ass.*, **151**, 347.
Kuhns, W. J., and McCarty, M. (1954). *J. clin. Invest.*, **33**, 759.
Kuttner, A. G., Baldwin, J. S., McEwen, C., Bunim, J. J., Ziff, M., and Ford, D. K. (1952). *J. Amer. med. Ass.*, **148**, 628.
Leader (1951a). *Lancet*, **1**, 780.
—— (1951b). *Brit. med. J.*, **2**, 162.
—— (1953). *Ibid.*, **1**, 278.
Macdonald, T. C. (1950). *Ibid.*, **1**, 992.
McVay, L. V., Jr., and Sprunt, D. H. (1953). *New Engl. J. Med.*, **249**, 387.
Medical Research Council and American Heart Association (1955). *Brit. med. J.*, **1**, 555.
Miller, J. M., Kibrick, S., and Massell, B. F. (1953). *J. clin. Invest.*, **32**, 691.
Ministry of Health (1953). "Annual Report of the Chief Medical Officer, 1951", Pt. III, p. 97.
Morris, J. N., and Titmuss, R. M. (1942). *Lancet*, **2**, 59.
——, —— (1944). *Med. Offr.*, **72**, 69, 77, 85.
Mote, J. R., and Jones, T. D. (1941). *J. Immunol.*, **41**, 35.
Parkinson, J. (1942). *Lancet*, **2**, 657.
Perry, C. B. (1940). *Arch. Dis. Childh.*, **15**, 177.
—— (1944). *Bristol med.-chir. J.*, **61**, 1.
——, and Gillespie, W. A. (1954). *Brit. med. J.*, **2**, 729.
Pickles, W. N. (1943). *Lancet*, **2**, 241.
Ryle, J. A. (1946). *J. roy. San. Inst.*, **66**, 277.
Sheinkopf, J. A., Griffith, G. C., Morrison, R., and Starr, P. (1952). *Amer. J. med. Sci.*, **224**, 390.
Sheldon, W. (1948). *Acta paediat.* (*Uppsala*), **36**, 383.
Stevenson, A. C., and Cheeseman, E. A. (1953). *Ann. Eugen.* (*Lond.*), **17**, 177.
Stollerman, G. H., and Rusoff, J. H. (1952). *J. Amer. med. Ass.*, **150**, 1571.
Todd, E. W., Coburn, A. F., and Hill, A. B. (1939). *Lancet*, **2**, 1213.
Uchida, I. A. (1953). *Amer. J. hum. Genet.*, **5**, 61.
Wannamaker, L. W., Rammelkamp, C. H., Denny, F. W., Brink, W. R., Houser, H. B., and Hahn, E. D. (1951). *Amer. J. Med.*, **10**, 673.
Wilson, M. G., Helper, H. N., Lubschez, R., Hain, K., and Epstein, N. (1953). *Amer. J. Dis. Child.*, **86**, 131.
——, and Lubschez, R. (1948). *J. Amer. med. Ass.*, **138**, 794.
——, and Schweitzer, M. (1954). *Circulation*, **10**, 699.

Tendences actuelles du rhumatisme aigu

RÉSUMÉ

Le nombre des décès de rhumatisme articulaire aigu en Angleterre et au pays de Galles a baissé de 1,251 en 1940 à 310 en 1953; les chiffres annuels d'après-guerre, estimés entre 4,000 et 5,000 cas nouveaux parmi les enfants d'âge scolaire, n'étaient qu'un tiers ou un quart de ceux d'avant-guerre.

L'infection streptococcique se trouve habituellement associée au rhumatisme articulaire aigu, mais elle n'y est un facteur exclusif. On a obtenu de bons résultats avec quelques méthodes de chimio-prophylaxie, mais leur emploi n'a pas été assez prolongé pour qu'on puisse les considérer comme un facteur significatif. Le traitement par la cortisone et par la Butazolidine s'est avéré décevant. Il n'y a pas eu d'expansion sur une grande échelle de centre spéciaux pour le rhumatisme.

L'hérédité peut jouer un rôle, mais les facteurs génétiques n'ont pas eu assez de temps pour acquérir de l'importance. Parmi les facteurs plus importants on trouve l'exposition à l'infection streptococcique et la pauvreté. L'importance du milieu est mise en évidence par l'étude de la fréquence du rhumatisme articulaire aigu dans les villes groupées selon le revenu et le pouvoir d'achat des habitants; on y observe encore de grandes différences malgré la baisse générale de la mortalité.

Tendencias actuales del reumatismo poliarticular agudo

SUMARIO

El número de muertes de reumatismo poliarticular agudo en Inglaterra y en el país de Gales bajó de 1·251 en 1940 a 310 en 1953; las cifras anuales después de la guerra, estimados entre 4·000 y 5·000 casos nuevos entre niños de escuela, representan tan sólo una tercera o una cuarta parte de las de antes de la guerra.

La infección estreptocóccica se ve generalmente asociada con el reumatismo poliarticular agudo pero no constituye un factor exclusivo. Se lograron buenos resultados con algunos métodos de quimioprofilaxis, pero éstos no fueron empleados durante un tiempo suficiente para constituirse en un factor significativo. El tratamiento con cortisona y con Butazolidina fué delusivo. No hubo expansión en gran escala de centros especiales para el reumatismo.

La herencia puede desempeñar un papel, pero los factores genéticos no tuvieron tiempo suficiente para alcanzar importancia. Entre los factores más importantes se destacan la exposición a la infección estreptocóccica y la pobreza. La importancia del medio se ve revelada por los estudios de la incidencia del reumatismo poliarticular agudo en ciudades agrupadas según los ingresos y el poder de compra, donde se observan todavía grandes diferencias a pesar de la baja general de la mortalidad.

Ann. rheum. Dis. (1956), **15**, 40.

SPONDYLITIS IN POST-PUBERTAL PATIENTS WITH RHEUMATOID ARTHRITIS OF JUVENILE ONSET*

BY

MORRIS ZIFF, VINCENT CONTRERAS†, and CURRIER McEWEN

From the Department of Medicine and the Study Group on Rheumatic Diseases, New York University College of Medicine

(RECEIVED FOR PUBLICATION JANUARY 20, 1956)

The involvement of the cervical spine in patients with juvenile rheumatoid arthritis was mentioned by Still (1897) as among the earliest manifestations of this disease. Middlemiss (1951) has reported that clinical involvement of the cervical spine, though observed frequently, is not as often seen radiologically. Coss and Boots (1946) found fusion of two or more cervical segments in 11 per cent. of their patients with juvenile rheumatoid arthritis. In an analysis of 61 cases, Barkin (1952) and Potter, Barkin, and Stillman (1954) found clinical involvement of the cervical spine in 70 per cent. of individuals, and obtained radiological confirmation in 54 per cent. The most frequent and outstanding radiological change was narrowing, irregularity, and often fusion of the apophyseal joints of two or more cervical vertebrae.

These observations have led us to review the *x* rays of the spine and sacro-iliac joints of our post-pubertal patients with rheumatoid arthritis in whom the disease had begun in childhood. This was done to determine whether it would be possible to utilize the presence of a characteristic type of spondylitis, if found with sufficient frequency in this group, as an aid in the retrospective diagnosis of juvenile rheumatoid arthritis in cases in which evidence of the childhood stage of the disease might have been clinically inapparent.

Material

Sixteen patients in the post-pubertal age group with rheumatoid arthritis of juvenile onset were studied. Their ages ranged from 12·5 to 50 years (average 23). Twelve were females and four males. Fifteen had had the disease for periods ranging from 5 to 47 years, and one had had it for one year. All gave a history of significant peripheral joint involvement in the early stages of the disease. As controls, the available spine *x* rays of 26 adult patients with clinical rheumatoid arthritis of more than 4 years' duration were reviewed.

Results

The *x*-ray findings were related to the history, clinical findings, and sensitized sheep cell agglutination titres (Table I, opposite).

Radiology.—One patient (Case 1) showed no significant radiological changes in the spine. Three (Cases 14, 15, 16) demonstrated in addition to peripheral arthritis the characteristic features of ankylosing spondylitis with involvement of the sacro-iliac and apophyseal joints, and calcification of paravertebral ligaments; two of these showed clinical and radiological involvement of the cervical spine of the type seen in this disease. The remaining twelve patients showed, in addition to peripheral arthritis, *x*-ray evidence of fusion of one or more cervical apophyseal joints. Thus, fifteen of the sixteen patients showed some form of spondylitis and fourteen showed cervical spine involvement. This demonstrates the high incidence with which the cervical spine is involved in the later stages of juvenile rheumatoid arthritis.

Fig. 1 (opposite) shows the changes of ankylosing spondylitis which are indistinguishable roentgenographically from the classical adult type in a 50-year-old female (Case 16) whose disease had begun peripherally at age 3. In addition to the cervical spine there were classical changes in the sacro-iliac joints, apophyseal joints, and paravertebral ligaments, as well as involvement of most peripheral joints.

* This work was supported by a grant from the Masonic Foundation for Medical Research and Human Welfare.

† Rockefeller Foundation Fellow. Present Address: Hospital Jose Joaquin Aquirre, University of Chile, Santiago, Chile.

TABLE I

CLINICAL AND RADIOLOGICAL FINDINGS AND SHEEP CELL AGGLUTINATION TITRES IN POST-PUBERTAL PATIENTS WITH RHEUMATOID ARTHRITIS OF JUVENILE ONSET

Case No.	Sex	Age (yrs)	Age at Onset of Disease (yrs)	Clinical and Radiological Involvement of Cervical Spine	Sheep Cell Agglutination Test	
					Euglobin Fraction	Inhibition†
1	F	17	10	−*	Positive	Absent
2	M	12·5	5	+	Positive	Absent
3	F	17	11	+	Positive	Absent
4	F	13	12	+	Positive	Absent
5	F	18	6	+	Positive	Absent
6	F	21	11	+	Positive	Absent
7	F	32	12	+	Test not done	Test not done
8	M	20	6	+	Negative	Absent
9	F	25	13	+	Negative	Absent
10	F	23	12	+	Positive	Absent
11	F	28	4	+	Negative	Absent
12	F	17	12	+	Negative	Absent
13	F	20	2·5	+	Negative	Absent
14	M	18	7	−	Negative	Absent
15	M	37	12	+	Negative	Present
16	F	50	3	+	Test not done	Test not done

* The spine was involved clinically but not radiologically.
† Absence of inhibition signifies presence of sheep cell factor.

Fig. 1.—Changes of ankylosing spondylitis; slight kyphosis of all apophyseal joints; thinning of all disk cartilages; calcification of paravertebral ligaments (Case 16, Table I).

In twelve patients (75 per cent.), however, there were isolated cervical lesions in which the most characteristic change was fusion of the apophyseal joint between C_2 and C_3 (Fig. 2, overleaf), and less often also between C_3-C_4, or even at a lower level (Fig. 3, overleaf).

Other radiological findings pointed out by Potter, Barkin, and Stillman (1954) have also been noted in this group, *i.e.* loss of normal cervical lordosis (Fig. 3), and even kyphosis; underdevelopment of the bodies (Figs 2 and 3); and thinning of the disk cartilages between the cervical vertebrae (Fig. 3). Fig. 4 (overleaf) shows progression of the lesion of the C_2-C_3 apophyseal joint in Case 5 during a 4-year period.

In three of the above twelve patients (Cases 2, 5, 7), the cervical spine involvement was accompanied by radiological changes in the sacro-iliac joints consisting of blurring of the joint space and some degree of subchondral sclerosis. Actual obliteration of the joint space was not observed. In Table II (overleaf) details of the radiological findings in the sixteen patients are presented.

Clinical Findings.—Pain and stiffness of the neck at some time were present in all patients but one (Case 14). In most cases, the presentation of

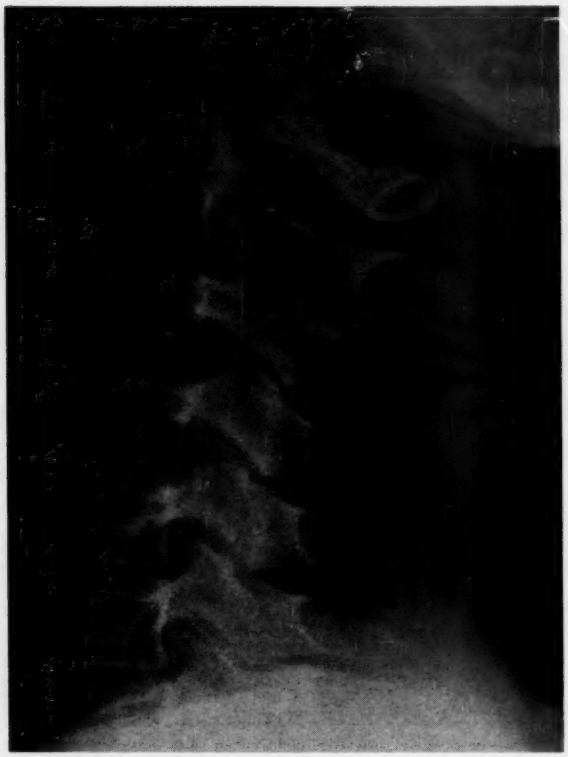


Fig. 2.—Fusion of apophyseal joints between C_2 and C_3; loss of normal lordosis; underdevelopment of bony structures (Case 2).

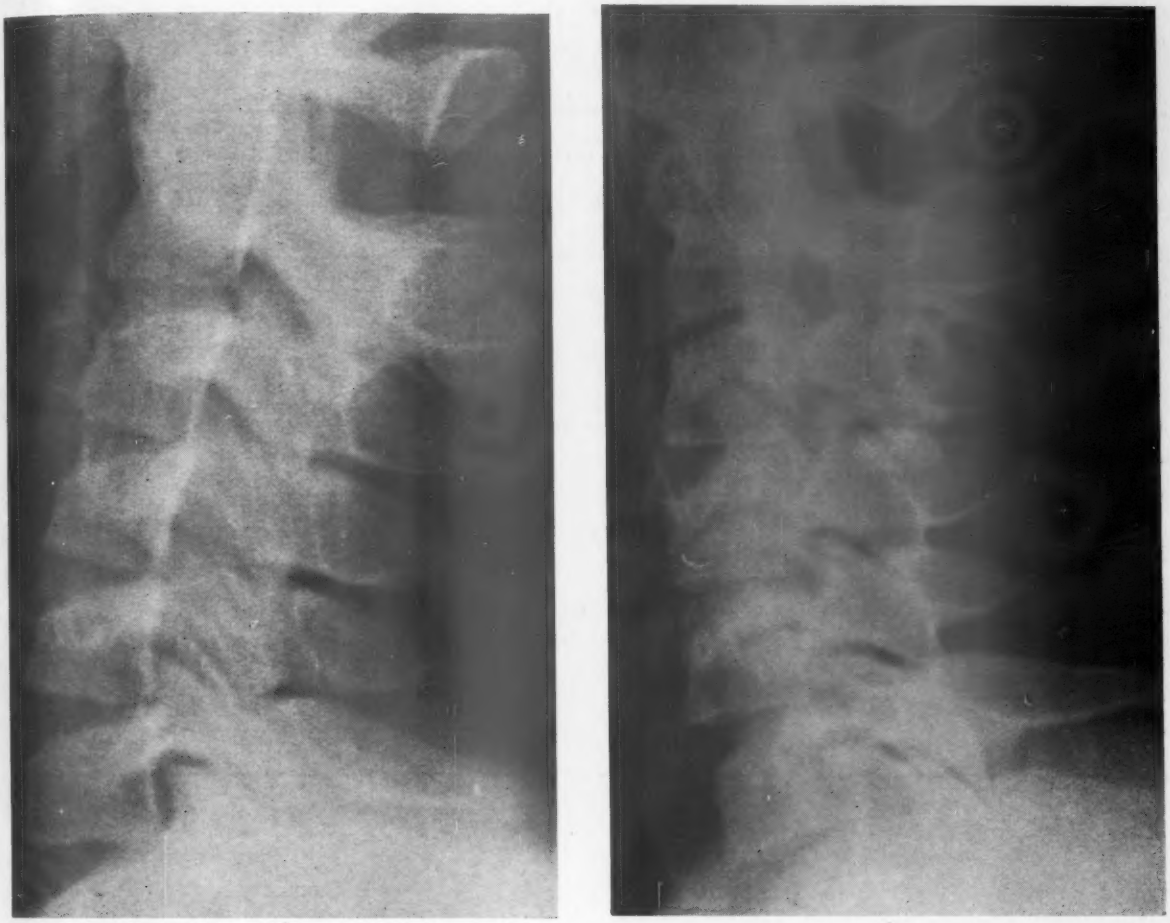
Fig. 3.—Fusion of apophyseal joints between C_2-C_3, C_3-C_4, and C_5-C_6; thinning of the disk cartilages between the same vertebrae; loss of cervical lordosis; underdevelopment of bony structures (Case 10).

symptoms of cervical spondylitis occurred early in the course of the disease; they were the first to be noted in three patients (Cases 2, 8, 9), and in the remainder the symptoms began in the peripheral joints. Significant limitation of motion of the cervical spine, as revealed by history or findings on physical examination, was present at some time in all but three patients (Cases 4, 6, 14); one of these (Case 14) was the patient with the ankylosing type of spondylitis sparing the cervical spine. The cervical pain usually disappeared after periods ranging from a few months to 4 years after onset, but stiffness and limitation of motion were residual in all the fourteen patients with cervical spine involvement but two (Cases 4 and 6).

Sensitized Sheep Cell Agglutination Titres.—This test was done in fourteen patients using the euglobin fraction for both direct agglutination and for inhibition of known positive sera (Ziff, Brown, Badin, and McEwen, 1954, 1956). Sheep cell agglutination tests were done in eleven of the twelve individuals with isolated cervical lesions. In six of these (Table I), the euglobin fraction, when tested directly, gave a positive result, and in all eleven the euglobin failed to inhibit known positive serum, indicating that the sheep cell factor was present.

The sheep cell agglutination test was done in two (Cases 14 and 15) of the three cases presenting the pattern of ankylosing spondylitis. The test was negative in Case 15. Though the euglobin fraction of Case 14 did not show agglutination in a significant titre, it did not inhibit known positive serum, indicating the presence of the sheep cell factor. The patient with no *x*-ray changes in the spine (Case 1) gave a positive sheep cell agglutination test.

Control Series.—We reviewed the *x* rays of the cervical spines of 26 patients with rheumatoid arthritis in the Out-Patient Clinic of Bellevue Hospital, who were known to the authors individually, and for whom *x* rays of the cervical and lumbosacral spine, and sacro-iliac joints were available. All had had the disease for more than 4 years and in all cases the disease was known to



(*a*) (*b*)

Fig. 4.—Progression of fusion of C_2-C_3 apophyseal joint in Case 5 during a 4-year period. (*a*) at age 14; (*b*) at age 18.

have begun after puberty. Seven were males and nineteen were females, and they ranged in age from 28 to 65 years. In this group, only two showed changes in the spine, and these consisted of fusion of the apophyseal joints localized at C_2-C_3 segments.

Discussion

The results of this study emphasize, as have previous investigations, the frequency of involvement of the spine in the juvenile type of rheumatoid arthritis. This involvement appears to be especially common, however, in the post-pubertal group of such patients, who are in the later stages of the disease. Fifteen of the sixteen patients studied showed radiological evidence of spondylitis of one form or another.

Most commonly this involvement presented itself as fusion of one or more cervical apophyseal joints as found in twelve of the individuals of the present group. The presence of the sheep cell factor in the serum of all these patients who were tested (as indicated by absence of inhibition of positive rheumatoid serum) indicates a relation to the classical type of peripheral rheumatoid arthritis and not to ankylosing spondylitis (Ziff, Brown, Badin, and McEwen, 1954, 1956). This is true in spite of the fact that three showed some degree of sacro-iliac involvement, which when it occurs with ankylosing spondylitis in adults is almost always associated with negative agglutination tests (Ziff and others, 1954, 1956).

In a minority of cases, the juvenile disease, at least as far as the spine was concerned, appeared to follow the pattern of adult ankylosing spondylitis, although peripheral joint involvement was the striking feature early in the disease. This was true in three of the sixteen cases. In such cases, apparently, the cervical spine may or may not become involved in the usually ascending progression of the disease. If the cervical spine is reached, the type of lesion

TABLE II

RADIOLOGICAL FINDINGS IN SPINE IN POST-PUBERTAL PATIENTS WITH RHEUMATOID ARTHRITIS OF JUVENILE ONSET

Case No.	Cervical Fusion	Loss of Lordosis	Under-development of Bony Structures	Thinning of Intervertebral Disks	Sacro-iliac Involvement	Calcification of Ligaments
1	—	−	−	—	−	−
2	C_2–C_3 C_7–D_1	+	+	C_2–C_3	+	−
3	C_2–C_3	−	+	—	−	−
4	C_2–C_3	+	−	—	−	−
5	C_2–C_3	+	−	C_3–C_6	+	−
6	C_2–C_3	−	−	—	−	−
7	C_2–C_3	+	−	—	+	−
8	C_2–C_4	+	+	C_3–C_4	−	−
9	C_2–C_7	+	−	C_2–C_7	−	−
10	C_2–C_4 C_5–C_6	+	+	C_2–C_5 C_6–C_7	−	−
11	C_2–C_3	−	−	C_2–C_3	−	−
12	C_7–D_1	+	−	—	−	−
13	C_2–C_4 C_7–D_1	−	+	C_2–C_4 C_7–D_1	−	−
14	—	−	−	—	+	+
15	C_2–C_7	−	−	C_2–C_7	+	+
16	C_2–C_7	+	+	C_2–C_7	+	+

+ = present − = absent

seen on *x* ray in this region is the same as that seen in adult ankylosing spondylitis, including calcification of paravertebral ligaments. The two cases in this group on the sera of which there was an opportunity to perform the sheep cell agglutination test are too few to allow any significant application of this test as an aid in deciding whether the group is related to classical rheumatoid arthritis or to ankylosing spondylitis.

The control group of 26 patients with rheumatoid arthritis whose disease began post-pubertally showed fusion of the C_2-C_3 apophyseal joint in two instances. The sacro-iliac joints were not abnormal in these patients. It appears, therefore, that though radiological evidence of spinal involvement of the type described may be found in adult rheumatoid arthritis, it is relatively infrequent. It may be that in some cases demonstrating such changes, the childhood stage of the disease had been missed. It appears, from the findings presented, that the presence of localized cervical spondylitis, especially fusion of apophyseal joints, in any particular individual with rheumatoid arthritis, justifies suspicion of a childhood onset of the disease.

Summary

Sixteen patients in the post-pubertal age group with rheumatoid arthritis of juvenile onset have been studied with respect to involvement of the spine. Clinical and radiological findings and the results of sensitized sheep cell agglutination tests have been correlated.

All patients had peripheral arthritis in the early stages of the disease. Fifteen of the sixteen demonstrated spinal involvement of one form or another, radiologically, at the time of the study. In three patients, this followed the pattern of ankylosing spondylitis as seen in adults, including in two of them the cervical spine. In twelve patients the outstanding change was fusion of the cervical apophyseal joints, especially the C_2-C_3 segments. The results of sensitized sheep cell agglutination tests resembled those obtained in adult peripheral rheumatoid arthritis rather than those in adult ankylosing spondylitis.

REFERENCES

Barkin, R. E. (1952). *Bull. rheum. Dis.*, 3, No. 1, p. 19.
Coss, J. A., and Boots, R. H. (1946). *J. Pediatr.*, 29, 143.
Middlemiss, J. H. (1951). *Proc. roy. Soc. Med.*, 44, 805.

Potter, T. A., Barkin, R. E., and Stillman, J. S. (1954). *Annals of the Rheumatic Diseases*, **13**, 364.
Still, G. F. (1897). *Med.-chir. Trans.*, **80**, 47.
Ziff, M., Brown, P., Badin, J., and McEwen, C. (1954). *Bull. rheum. Dis.*, **5**, 75.
——, ——, ——, —— (1956). *Amer. J. Med.* In the press.

La spondylarthrite des malades pubères atteints d'arthrite rhumatismale à début juvénil

RÉSUMÉ

On étudia l'atteinte vertébrale de l'arthrite rhumatismale à début juvénil chez seize malades pubères, à la lumière des résultats cliniques, radiologiques et de la réaction d'agglutination des cellules de mouton sensibilisées.

L'atteinte articulaire périphérique exista chez tous les seize malades dès la période de début. A l'examen on décéla des signes radiologiques de l'atteinte vertébrale chez 15 d'entre eux. Chez trois malades cette atteinte correspondit à l'image de la spondylarthrite de l'adulte, y compris l'implication cervicale chez deux d'entre eux. Dans douze cas la fusion des apophyses cervicales, surtout au niveau C2-C3, fut la lésion la plus importante. Les chiffres de la réaction d'agglutination des cellules de mouton s'approchèrent plus à ceux de la polyarthrite de l'adulte qu'à ceux de la spondylarthrite ankylosante de l'adulte.

La espondilartritis en enfermos púberos con artritis reumatoide adquirida en infancia

SUMARIO

Se estudió el compromiso vertebral de la artritis reumatoide con comienzo juvenil en dieciseis enfermos púberos, a la luz de los resultados clínicos, radiológicos y de la reacción de aglutinacion de las células sensibilizadas de oveja.

Todos los enfermos sufrieron de artritis periférica desde el comienzo de la enfermedad. En quince de ellos el compromiso vertebral en alguna forma fué demostrado radiológicamente al tiempo del estudio. En tres de éstos se trató de la espondilartritis anquilosante semejante a la del adulto, incluyendo en dos de ellos la espina cervical. En doce casos la fusión de las apofisis cervicales, en particular al nivel de C2-C3, fué la lesión la más importante. Las cifras de la reacción de aglutinación de las células de oveja se aproximaron más a las de la poliartritis del adulto que a las de la espondilartritis anquilosante del adulto.

Ann. rheum. Dis. (1956), **15**, 46.

HYPERTROPHIC OSTEO-ARTHROPATHY IN POLYARTERITIS

BY

R. R. H. LOVELL AND G. B. D. SCOTT

From the Medical Unit and Department of Morbid Anatomy, St. Mary's Hospital, Paddington

(RECEIVED FOR PUBLICATION AUGUST 16, 1955)

Hypertrophic osteo-arthropathy is most commonly associated with bronchopulmonary or pleural diseases. It has also been described in several apparently unrelated conditions and occasionally in patients with no other recognizable disease. The literature is reviewed by Mendlowitz (1942). This paper reports hypertrophic osteo-arthropathy in a patient with polyarteritis nodosa and describes the effect of cortisone.

Case Report

A male business executive, aged 51, had suffered no serious illness until 1947, when he started to get aching pains in the backs of the thighs; the pains were constant, and worse when he was tired, but unaffected by movement. Early in 1948 his right ankle became swollen and he developed painful red papules, up to 3 mm. diameter, some of which ulcerated. About this time purple mottling was noticed on the legs and forearms. Later in 1948 his knees became swollen and painful but he was able to play golf. Early in 1949 the wrists, elbows, and metacarpo-phalangeal joints were painful and swollen and he suffered increasingly severe limb pains unrelated to joints. During 1950 he was disabled by pain, for which he took up to 24 tablets codeine co. B.P. daily. He now noticed small nodules under the skin; he sweated profusely and lost about 7 lb. weight in 6 months. Apart from symptoms of a sudden right subclavian venous thrombosis while playing golf in 1949, his symptoms from 1947 to 1950 related only to the skin and locomotor system. He was seen in 1950 by Dr. W. S. C. Copeman and Dr. G. B. Mitchell-Heggs and was admitted to St. Mary's Hospital with a suggested diagnosis of polyarteritis nodosa.

Clinical Examination.—On admission in November, 1950, his limbs were very painful. There was swelling round the elbows, wrists, metacarpo-phalangeal, knee, and ankle joints. The swelling was due partly to synovial effusions, but there was also conspicuous peri-articular thickening extending 2-3 inches beyond the joints. The wrists, knees, and ankles were warm, but movements were free. There was slight clubbing of the fingers.

The skin showed three types of lesion typical of polyarteritis:

(*a*) purple mottling, most marked on the distal parts of the arms and legs;
(*b*) tender punched-out ulcers over the buttocks and scars of similar lesions which had healed;
(*c*) subcutaneous nodules about 3 mm. diameter on the forearms.

Apart from dilated superficial collateral veins consistent with an occlusion of the right subclavian vein, the other systems appeared healthy. The blood pressure was 105/65 mm. Hg.

Laboratory Investigations

Blood: Erythrocyte sedimentation rate (Westergren) 75 mm./1 hr.

Haemoglobin 11·1 g./100 ml., 3,800,000 red cells/c. mm., 15,000 white cells/c. mm. with 75 per cent. neutrophils, 19 per cent. lymphocytes, 3 per cent. eosinophils and 3 per cent. monocytes.

Urine: No abnormality.

Radiology: Appearance of heart and lungs normal. Hands, wrists, and elbows showed no joint changes. Knees showed some osteophytic lipping. Lower ends of shafts of forearm bones showed minimal irregular formation of new sub-periosteal bone (Fig. 2a, opposite).

Biopsy: Diagnosis of polyarteritis confirmed by finding of typical necrotizing arteritis in sections of a subcutaneous nodule (Fig. 1, opposite).

Clinical Course.—Treatment was started with corticotrophin 100 mg. daily by intramuscular injection. Within 4 days all limb and joint pains had gone, by the second week there was no joint swelling, and by the third week the skin ulcers had healed. The erythrocyte sedimentation rate fell to normal by the fourth week. The dose of corticotrophin was reduced to 50 mg. daily in the fifth week, following which there was a recurrence of limb pains and fresh skin lesions appeared; the biopsy of one of these again showed active polyarteritis.

During the next 3 years the patient was maintained on an average dose of 100 mg. cortisone daily. Despite some limb pain and joint swelling he lost no time from work and was able to play golf twice a week. After 3 years, however, ulcers developed around the ankles and on the legs; patches of skin on his feet became cold and blue, and the arterial pulses in the feet diminished. The ulcers enlarged and deepened, exposing muscles and tendons over areas up to 16 cm. across. Their expansion appeared unaffected by increasing the dose of cortisone to 400 mg./day, though on this dose all synovial effusions and periarticular swellings disappeared, and limb pains, other than those arising in the ulcers, disappeared. However, the pain in the extending ulcers became intolerable and the left leg was amputated above the knee in July, 1954, by Professor C. G. Rob, and 9 days later the patient died with a pulmonary embolus.

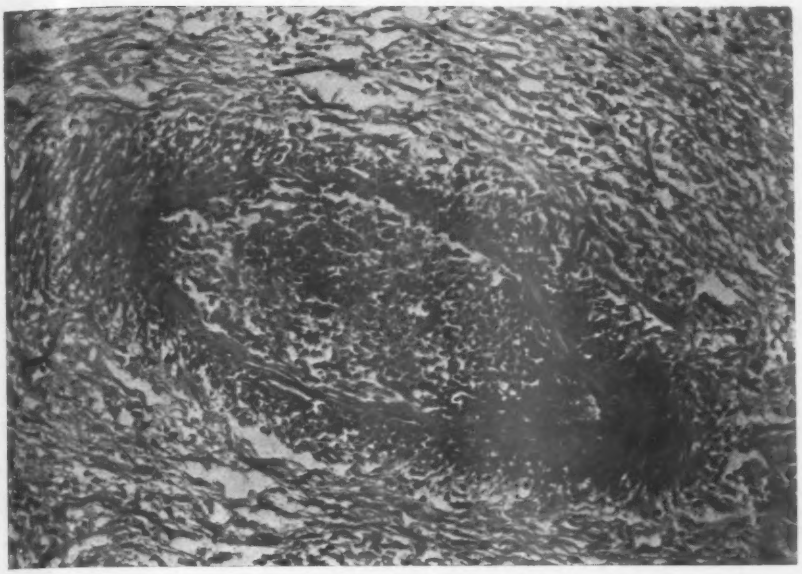


Fig. 1.—Artery showing inflammation and necrosis in a section through a subcutaneous nodule removed in December, 1950.

Up to the time of death there had been no clinical or radiological evidence of disease in the heart or lungs. During 3½ years of cortisone treatment the blood pressure rose steadily from 105/65 mm. Hg to 165/105 mm. Hg, though the only evidence of renal abnormality in this period was the finding twice of a few red cells and once of a few granular casts in fifteen examinations of urine deposit. Symptoms and signs relating to the joints had been suppressed for 3 months before death.

Radiological Changes in Joints and Bones.—The joints of the hands, wrists, knees, and ankles were examined radiologically at intervals from 1950 to 1954; there were no changes in them other than those associated with synovial effusions.

Fig. 2(*a*).—Right radius and ulna, showing minimal periosteal proliferation in 1950.

Fig. 2(*b*).—Right radius and ulna, showing more advanced periosteal changes in 1953.

Fig. 3.—Right tibia and fibula, showing periosteal changes in 1953.

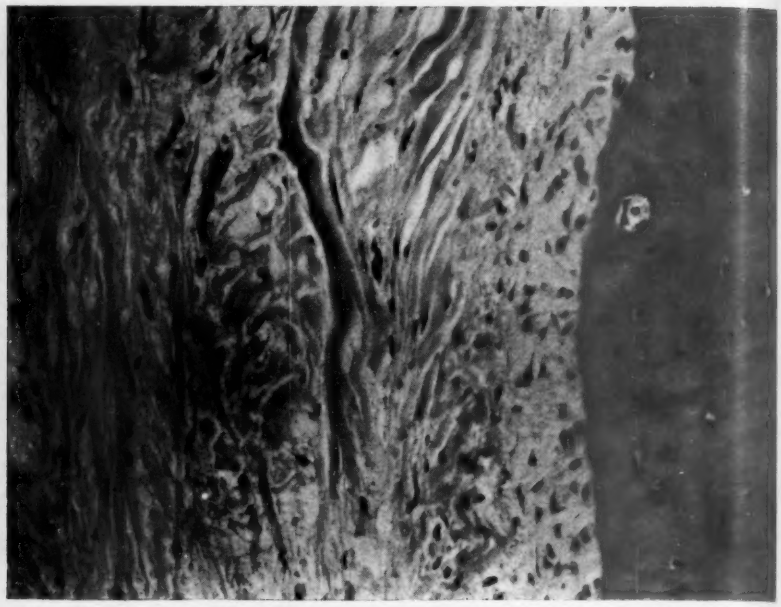


Fig. 4.—Thickened periosteum over a nodule excised at necropsy (× 180).

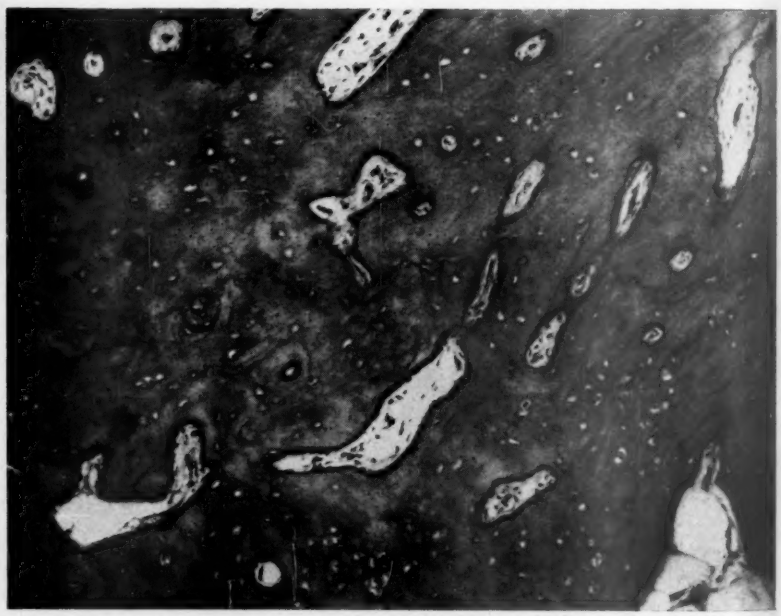


Fig. 5.—Irregular subperiosteal bone in same nodule as Fig. 4 (× 100).

The first extensive examination of the long bones was made in 1952, when changes were disclosed similar to those found in the forearms in 1950; subperiosteal new bone was now more conspicuous in the forearm bones and was present also in the tibiae and fibulae. A comparison of the appearances of the right radius and ulna in 1950 and 1953 shows that changes progressed during this period (Fig. 2). The appearances of the right tibia and fibula in 1953 are shown in Fig. 3.

Necropsy Findings.—An embolus occluded both main branches of the pulmonary artery. No active polyarteritis was found; two healed arterial lesions had been found in the skin of the amputated leg. The ulcers on the legs showed non-specific inflammation and were surrounded by dense fibrous tissue. The liver was pale and fatty, a change commonly seen in Cushing's syndrome and in patients receiving large doses of cortisone. The other viscera were normal.

Pathology of Joints and Bones.—Dissection of the knees and ankles showed much peri-articular fat. Otherwise their macroscopic appearances were normal. On microscopy the synovial membranes and articular surfaces were normal.

A nodular area was excised from the anterior surface of the lower part of the left tibia. The periosteum showed a clear division into two layers but there was no inflammatory reaction (Fig. 4). Beneath the periosteum there was a layer of newly-formed bone, showing no regular structure (Fig. 5). The appearance was in striking contrast to the lamellated compact bone of the underlying cortex (Fig. 6).

Discussion

Symptoms relating to the joints are common in polyarteritis and conform usually to one of two types (Lovell and Rose, 1955). There is either an acute, transient, sometimes migratory, arthritis, or a more chronic deforming arthritis resembling rheumatoid disease. Both types of arthritis are suppressed by cortisone. There is no doubt that this patient had polyarteritis, for the skin biopsies were unequivocal as were the appearances of the skin lesions. While the joint lesions might have been due to polyarteritis, their clinical features were typical of hypertrophic osteo-arthropathy. The associated finger clubbing and radiological and pathological changes in the bones show that hypertrophic osteo-arthropathy was indeed present.

The histological appearances in the joints and bones differed from those described in hypertrophic osteo-arthropathy by Gall, Bennett, and Bauer (1951) in only one respect, namely the absence of inflammatory changes in the joint tissues and in the periosteum. We confirmed the observation of these authors that inflammatory changes with lymphocytic infiltration are normally features of osteo-arthropathy by examining the tibial periosteum from a male aged 48 who died with this disease associated with a bronchial carcinoma. Fig. 7 shows a typical portion of periosteum from the tibia of this patient; the lymphocytic reaction contrasts strongly with the appearance in our patient (Fig. 4). Since, in our patient, cortisone had suppressed the clinical manifestations of joint inflammation and the limb pains for 3 months before he died, it seems likely that the absence of the inflammatory component of osteo-arthropathy on histological examination may be attributed to the effect of cortisone. With the doses of cortisone used, the irregular deposition of new cortical bone progressed.

Fig. 6.—Normal lamellated bone underlying periosteal nodule (× 100).

Fig. 7.—Lymphocytic reaction in periosteum of a patient with hypertrophic osteo-arthropathy who did not receive cortisone (× 180).

Summary

The occurrence of hypertrophic osteo-arthropathy is described in association with polyarteritis. Cortisone suppressed the arthritis and probably suppressed the inflammatory component of the periosteal reaction.

We thank Prof. G. W. Pickering and Dr. G. B. Mitchell-Heggs for permission to report this case.

REFERENCES

Gall, E. A., Bennett, G. A., and Bauer, W. (1951). *Amer. J. Path.*, 27, 349.
Lovell, R. R. H., and Rose, G. A. (1955). *Postgrad. med. J.*, 31, 382.
Mendlowitz, M. (1942). *Medicine (Baltimore)*, 21, 269.

Ostéoarthropathie hypertrophique dans la polyartérite

RÉSUMÉ

On décrit l'incidence de l'ostéoarthropathie hypertrophique en association avec la polyartérite. La cortisone supprima l'arthrite et, probablement, le composant inflammatoire de la réaction périostique.

Osteoartropatia hipertrófica de la poliarteritis

SUMARIO

Se describe la ocurrencia de la osteoartropatia hipertrófica en asociación con la poliarteritis. La cortisona suprimió la artritis y, probablemente, el componente inflamatorio de la reacción perióstica.

Ann. rheum. Dis. (1956), **15**, 51.

CLINICAL TRIAL OF INTRAVENOUS AND INTRAMUSCULAR IRON IN RHEUMATOID ARTHRITIS

BY

J. B. MILLARD AND H. STUART BARBER

From the Royal Devonshire Hospital, Buxton

(RECEIVED FOR PUBLICATION JUNE 8, 1955)

The common association of an anaemia with rheumatoid disease has been recognized for many years. It was commented upon by Glover (1928) and statistical confirmation was furnished by the Empire Rheumatism Council (1950). At one time thought to be the result of toxic absorption from the same infective focus producing the arthritis, the cause of the anaemia remains as obscure as that of the disease. As Sinclair and Duthie (1950) point out, a toxic depression of the bone marrow is not likely to be corrected by iron. It was suggested by Robinson (1943) that haemodilution occurred in the disease, but his methods of measuring blood volume have since been shown to be erroneous (Jeffrey, 1953). The anaemia is almost always hypochromic and recent studies indicate two possible aetiological factors, defective absorption of iron from the gut and a greatly increased demand for iron by some tissue or tissues as yet unidentified.

Whatever the cause, it is generally agreed that the restoration of the haemoglobin level to values as near normal as possible is an essential part of the treatment of rheumatoid disease. The prolonged administration of iron by mouth has not proved very effective (Ross, 1950). Blood transfusions have been given with good results, but the improvement has been transient (Simpson, Kersley, and Brooks, 1949). Iron given by the intravenous route has been shown to produce a more prolonged rise in the haemoglobin level (Sinclair and Duthie, 1950), but the difficulty of giving such injections to patients with joint deformities is a drawback as well as the liability to cause unpleasant side-reactions (Nissim, 1954). Furthermore, parenteral iron therapy in this form is not practicable in busy general practice. Clearly, an iron preparation for intramuscular injection free from side-effects and fairly rapidly absorbed would be a great advantage. This paper describes a clinical experiment to assess the relative value of oral iron against intravenous iron and of intravenous iron against intramuscular iron in the treatment of the anaemia of rheumatoid disease.

The oral iron used was ferrous gluconate in tablets of 300 mg. The intravenous preparation of iron (Ferrivenin) contains 20 mg. Fe per ml. and the intramuscular preparation (Imferon)* contains 50 mg. Fe per ml.

One hundred patients (92 females and 8 males) suffering from rheumatoid disease admitted to the wards of the Devonshire Royal Hospital were selected according to their haemoglobin level after an initial period of 2 weeks in hospital. It was found advisable to wait for this period, since some patients show a spontaneous rise in the haemoglobin level after a short period of hospital treatment, attributable perhaps to rest and change of diet. Estimations were carried out on admission and approximately 2 weeks later, and then at intervals of 4 weeks. Iron therapy was started during the third week in hospital.

A photo-electric absorptiometer was used to ascertain the haemoglobin percentage, taking 100 per cent. as equivalent to 14·8 g. haemoglobin per 100 ml. The erythrocyte sedimentation rate was recorded at the same time as the haemoglobin by the Westergren technique.

Method

The experiment was divided into two series. Series 1, consisting of fifty patients who had a haemoglobin level of 70 per cent. (10·4 g.) or less after 2 weeks in hospital, was divided into two groups of 25 each, the subjects being placed alternately into Group A or Group B. Group A were given oral ferrous gluconate in tablets of 300 mg. thrice daily for 30 days. Group B were given intravenous iron to a total of 1,500 mg. over a period of 8 days.

Series 2, comprising fifty patients who had a haemoglobin level of 80 per cent. (11·9 g.) or less, was also

* Manufactured by Bengers Ltd.

divided into two groups of 25. Group C was treated with intravenous iron to a total quantity of 1,500 mg. in 8 days. Group D was given intramuscular iron, the total dosage being calculated by multiplying the haemoglobin deficit by 25 and adding 250 mg. as recommended by the manufacturers.

Results

Haemoglobin

Series 1, Group A (Table I).—The oral iron group has a small average haemoglobin increase of 6·4 per cent. which remained virtually unaltered throughout the observation period. Six patients show a rise of 10 per cent. or more at 6 weeks and seven had a similar rise at 10 weeks. The results at 2 and 6 weeks show statistically significant difference.

Group B (Table I).—Four subjects had to be withdrawn from this group as they could not be followed up, but the remainder show an increase in the average haemoglobin level of 18·4 per cent. at 6 weeks and 24·6 per cent. at 10 weeks. All patients in this group responded, nineteen having a rise of 10 per cent. or over at 6 weeks and all maintaining the increase at 10 weeks. The results at 14 weeks are too few to analyse. The results at 2 and 6 weeks show a statistically significant difference.

Series 2, Group C (Table I).—Three subjects could not be followed up and had to be withdrawn. Among the remainder a rise of 10 per cent. or more in the haemoglobin occurred in ten cases at 6 weeks and in twelve cases at 10 weeks. Three patients showed no response. The average haemoglobin increase was 8·8 per cent. at 6 weeks and 14·4 per cent. at 10 weeks. The results at 2 and 6 weeks show a statistically significant difference.

Group D (*Table I*).—Nine patients show a rise in haemoglobin of 10 per cent. or more at 6 weeks and nine had a similar rise at 10 weeks. Seven patients failed to give any response. The average increase was 8·2 per cent. haemoglobin at 6 weeks and 8·9 per cent. at 10 weeks. The figures at 14 weeks are insufficient to analyse. The results at 2 and 6 weeks show a statistically significant difference.

Erythrocyte Sedimentation Rate (Table II, opposite).—The results are given in a simplified form showing the distribution curve, average erythrocyte sedimentation rate, and range for each group.

Series 1, Group A.—There is very little change in the average erythrocyte sedimentation rate. Three subjects had a rise of over 30 per cent. and four subjects a fall of over 30 per cent. at the 6th week, as compared with the 2nd week. The distribution curve shows a slight improvement at the 10th week, but five of the subjects with a high erythrocyte sedimentation rate previously (over 80 mm.) were not available at this estimation period. The overall picture is a slight improvement. There is no statistical difference at 2 and 6 weeks.

Group B.—The average erythrocyte sedimentation rate fell by 16·5 per cent. at the 6th week and a further 9 per cent. at the 10th week. Six subjects had an improvement of over 30 per cent. No subjects deteriorated. The distribution curves show a gradual improvement. Of the four subjects not

TABLE I

HAEMOGLOBIN PERCENTAGES

Series	Group	Time since Admission (wks)	0	2	6	10	14
1	A Oral	Mean	71·0	64·8	71·2	73·4	72·2
		Range	53–81	56–70	57–84	62–90	—
		Standard Deviation	—	±4·04	±6·42	—	—
		No. of Observations	13	25	25	20	10
	B Intravenous	Mean	68·6	64·0	82·4	88·6	83·5
		Range	59–83	50–70	72–96	72–104	—
		Standard Deviation	—	±4·87	±5·76	—	—
		No. of Observations	13	21	21	17	12
2	C Intravenous	Mean	71·0	71·7	80·5	86·1	87·6
		Range	54–80	60–77	65–90	62–102	—
		Standard Deviation	—	±4·68	±6·15	—	—
		No. of Observations	22	22	22	19	10
	D Intramuscular	Mean	73·3	71·8	80·0	80·7	84·0
		Range	55–87	51–80	64–93	73–98	—
		Standard Deviation	—	±7·80	±6·48	—	—
		No. of Observations	24	25	25	22	11

TABLE II

ERYTHROCYTE SEDIMENTATION RATES
(mm./hr Westergren)

Group	Series	E.S.R. (mm./hr.)	Time since Admission (wks)				
			0	2	6	10	14
(1)	A Oral	0–19	1	0	1	1	0
		20–39	1	4	1	2	2
		40–59	2	4	8	7	2
		60–79	1	5	3	4	2
		80–99	7	9	8	3	2
		100 and over	1	3	4	3	2
		Total	13	25	25	20	10
		Average	71	71	70	65	69
	B Intravenous	0–19	0	0	1	1	0
		20–39	3	5	6	4	2
		40–59	5	5	6	7	6
		60–79	0	4	3	3	1
		80–99	2	2	2	1	2
		100 and over	3	5	3	1	0
		Total	13	21	21	17	11
		Average	62	66	55	49	53
(2)	C Intravenous	0–19	0	0	2	3	0
		20–39	4	6	7	5	2
		40–59	8	7	3	6	8
		60–79	6	6	10	4	1
		80–99	5	5	2	3	1
		100 and over	1	1	1	1	0
		Total	24	25	25	22	12
		Average	60	62	51	49	49
	D Intramuscular	0–19	0	0	1	0	0
		20–39	3	5	7	5	2
		40–59	6	3	6	4	2
		60–79	1	6	1	3	2
		80–99	7	4	5	2	2
		100 and over	5	4	2	4	2
		Total	22	22	22	18	10
		Average	72	66	55	63	70

seen at the 10th week, two had a high erythrocyte sedimentation rate (80-90 mm.) and two had a low erythrocyte sedimentation rate (20-39 mm.) previously. The overall picture is one of improvement. The results at 2 and 6 weeks are significantly different.

Series 2, Group C.—At the 6th week the average erythrocyte sedimentation rate fell by 17·5 per cent., but returned to its previous level at the 10th week. Four subjects had left the group at the 10th week; of these, three had an erythrocyte sedimentation rate of under 40, and the other was 40 at the 6th week. The distribution curve, when adjusted, shows an improvement. Eight subjects had an improvement of over 30 per cent. and one deteriorated by 30 per cent. at the 6th week. The overall picture is one of slight improvement. The result at 2 and 6 weeks show a statistically significant difference.

Group D.—The average erythrocyte sedimentation rate fell by 17 per cent. at the 6th week and remained unchanged. The distribution curves show an improvement. The three subjects not estimated at the 10th week had an erythrocyte sedimentation rate of 40, 60, and 65 at the previous estimation. Five subjects had a 30 per cent. improvement and two a 30 per cent. deterioration at 6 weeks.

The overall picture is one of improvement. The results at 2 and 6 weeks are significantly different statistically.

Discussion

The results show that oral iron has little effect on the anaemia of rheumatoid disease, thus confirming the work of others. Intravenous iron evokes a good response with an increase in the haemoglobin and some improvement in the sedimentation rate. In the second series, starting with a higher initial haemoglobin, both groups show an increase, but at the 10th week the patients on intravenous iron were somewhat better. Nevertheless, if cases with an initial haemoglobin of 70 per cent. (10·4 g.) or under are compared, the average increase in Groups C and D is about 14 per cent., which is much the same as Group B, the intravenous group of the first series. Seven patients failed to respond to intramuscular iron compared with three in the intravenous iron groups. It must be concluded that intramuscular iron in the dosage given is more likely to produce a response than oral iron, but is less likely to be effective than intravenous iron. The total quantity of intramuscular iron was rather less than that given intravenously and this may account for the variation in effect. As there were no significant reactions with the intramuscular preparation there seems no contra-indication to augmenting the total amount by giving it over a long period.

Group A may be taken as a rough control group for comparison with intravenous and intramuscular iron medication, since so little alteration occurred in the haemoglobin levels.

Other workers (Sinclair and Duthie, 1949, 1950; Jeffrey, 1953; Ross, 1950) have suggested that a fall in the erythrocyte sedimentation rate occurs when the response is good to parenteral iron. Of the 29 patients who showed a rise of 10 per cent. or more in the haemoglobin level after intravenous iron, and of the nine who showed a similar response to intramuscular iron, sixteen had a high erythrocyte sedimentation rate (over 60 mm.) and 22 had a moderately raised erythrocyte sedimentation rate. Thirteen of these cases showed an improvement of over 30 per cent. in the erythrocyte sedimentation rate, 24 remained unaltered, and one deteriorated by over

30 per cent. (Of the thirteen cases, the initial erythrocyte sedimentation rate was high in six and moderately raised in seven.) This does not indicate any clear relationship between the haemoglobin and the sedimentation rate, nor was it found that the best results with parenteral iron occurred in patients with a low initial erythrocyte sedimentation rate.

Conclusion

The results of the observations in this series show that oral iron is of little value in the treatment of the anaemia of rheumatoid arthritis and that intramuscular iron and intravenous iron are both effective and give similar benefit.

It is suggested that intramuscular iron should be tried in larger doses.

Summary

(1) One hundred cases of rheumatoid arthritis with anaemia were treated by one of three methods:

(*a*) 25 subjects were given 300 mg. ferrous gluconate orally for one month;

(*b*) Fifty subjects were given intravenous iron (1,500 mg.);

(*c*) 25 subjects were given intramuscular iron (1,000 mg.).

(2) The resulting haemoglobin and erythrocyte sedimentation rate changes were analysed.

(3) It is concluded that oral iron has little value in the treatment of the anaemia of rheumatoid arthritis, and that intramuscular iron is as beneficial as intravenous iron and easier to administer.

We should like to acknowledge the help of Dr. L. Delicati (Resident Medical Officer), and thank the Medical Director, Research Department, Bengers Ltd., for supplies of Imferon.

REFERENCES

Empire Rheumatism Council (1950). Report of Scientific Advisory Committee, *Annals of the Rheumatic Diseases*, 9, Suppl.
Glover, J. A. (1928). Ministry of Health Reports on Public Health and Medical Subjects, No. 52. H.M.S.O., London.
Jeffrey, M. R. (1953). *Blood*, 8, 502.
Nissim, J. A. (1954). *Brit. med. J.*, 1, 352.
Robinson, G. L. (1943). *Annals of the Rheumatic Diseases*, 3, 207.
Ross, D. N. (1950). *Ibid.*, 9, 358.
Simpson, N. R. W., Kersley, G. D., and Brooks, D. Hall (1949). *Ibid.*, 8, 277.
Sinclair, R. J. G., and Duthie, J. J. R. (1949). *Lancet*, 2, 646.
——, —— (1950). *Brit. med. J.*, 2, 1257.

Essai clinique du fer intraveineux et intramusculaire dans l'arthrite rhumatismale

RÉSUMÉ

(1) Cent cas d'arthrite rhumatismale avec de l'anémie furent traités par une des trois méthodes suivantes:

(*a*) 25 sujets reçurent 30 cgr. de gluconate de fer trois fois par jour pendant un mois par voie buccale.

(*b*) 50 sujets reçurent du fer intraveineux (1 g. 50).

(*c*) 25 sujets reçurent du fer intramusculaire (1 g.).

(2) On analysa les chiffres consécutifs de l'hémoglobine et de la sédimentation globulaire.

(3) On conclut que le fer par voie buccale a peu de valeur dans le traitement de l'anémie de l'arthrite rhumatismale, et que le fer intramusculaire ne cède en rien au fer intraveineux, tout en étant plus facile à administrer.

Ensayo clínico del hierro endovenoso e intramuscular en la artritis reumatoide

SUMARIO

(1) Cien casos de artritis reumatoide con anemia fueron tratados con uno de los tres métodos siguientes:

(*a*) 25 sujetos recibieron 30 cgr. de gluconato de hierro tres veces al día durante un mes por vía oral.

(*b*) 50 sujetos recibieron hierro endovenoso (1·5 g.).

(*c*) 25 sujetos recibieron hierro intramuscular (1 g.).

(2) Se analizaron las variaciones resultantes de las cifras de hemoglobina y de sedimentación eritrocitaria.

(3) Se concluye que el hierro oral tiene poco valor en el tratamiento de la anemia de la artritis reumatoide, y que el intramuscular es tan beneficioso como el endovenoso, además de su administración más fácil.

Ann. rheum. Dis. (1956), **15**, 55.

RADIOLOGICAL SIGNS OF RHEUMATOID ARTHRITIS

A STUDY OF OBSERVER DIFFERENCES IN THE READING OF HAND FILMS

BY

J. H. KELLGREN

WITH THE ASSISTANCE OF FRIDA BIER

From the Rheumatism Research Centre, University of Manchester

(RECEIVED FOR PUBLICATION JANUARY 2, 1956)

Radiological changes in the hands and feet have long been considered a useful aid in the diagnosis of rheumatoid arthritis. In a recent study, Fletcher and Rowley (1952) defined these changes in great detail. They confirmed the generally accepted opinion as to the value of surface and pocketed articular erosions, but found osteoporosis difficult to assess even with the help of a control bone as advocated by Steven (1947). Alterations in joint space, though common, may also be difficult to assess.

Defined gradings of these *x*-ray changes are being used as diagnostic aids in epidemiological studies of the prevalence of rheumatoid arthritis in different populations (Miall, Caplan, Cochrane, Kilpatrick, and Oldham, 1953; Miall, 1955) and similar radiological gradings have been used in therapeutic trials.*

It has therefore become necessary to know more about the reproducibility of such *x*-ray gradings by any given individual, and also the degree of inter-observer variance in the interpretation of individual films, since these factors have been shown to be important in the interpretation of chest films (Fletcher and Oldham, 1949; Yerushalmy, Harkness, Cope, and Kennedy, 1950; Yerushalmy, Garland, Harkness, Hirsshaw, Miller, Shipman, and Zwerling, 1951; Cochrane, Campbell, and Stein, 1949; Cochrane and Garland, 1952). The results reported by Miall (1953, 1955), however, suggest that the observer error in reading *x* rays of the hands and feet for rheumatoid arthritis may not be very great.

* Two trials comparing cortisone and aspirin therapy in rheumatoid arthritis, organized by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases (1954, 1955), and by the Empire Rheumatism Council (1955) respectively.

Materials and Method

Three sets of *x* rays have been studied. The first comprises 192 films of the hands obtained from sixty patients with early rheumatoid arthritis who were participating in a comparative study of the value of cortisone and aspirin therapy organized by the Joint Committee of the Medical Research Council and Nuffield Foundation (1954, 1955). In this group there were 24 males and 36 females with ages ranging from 17 to 59 years. The differential sheep cell agglutination test (D.A.T.), done by the method of Rose, Ragan, Pearce, and Lipman (1948), or that of Ball (1950), was positive in nearly three-quarters of the patients and all films were taken while the duration of the disease was less than 3 years. These films were read independently by six different observers with considerable experience in the diagnosis of rheumatoid arthritis: four clinicians (Observers I, II, III, and IV) and two radiologists (Observers V and VI). Osteoporosis and erosions which included narrowing of joint space were recorded separately and graded as follows:

None (0),
Doubtful (1),
Slight (2),
Moderate (3),
Severe (4).

In addition, one of the clinicians (Observer I) read the films a second time, using a single but similar grading for rheumatoid change as a whole, incorporating porosis, erosions, and alterations in joint space.

The second set of films was taken from a sample of the town population of Leigh, Lancs, including only those in the age group 55-64 years, who were *x*-rayed irrespective of symptoms. There were originally 173 men and 207 women in the sample, but only those with some evidence suggestive of rheumatoid disease either clinical, radiological, or serological were included in this study of *x*-ray readings. This gave 126 films of the hands from 41 men and 85 women, the D.A.T. being positive in nineteen of these individuals. These films were read

three times by the clinician (Observer I) who carried out the double reading in the first set of films.

The third set of films comprised 259 hands taken from a sample of an urban population in South Wales in which only individuals with clinical polyarthritis were *x*-rayed. This sample included all age groups and was derived from 88 males and 171 females. These films were read twice by Observer I, but there was an interval of over one year between the first and second reading.

Observer I has so far been mainly responsible for reading films in the rheumatological survey work being carried out by the Pneumoconiosis Research Unit and the Manchester Rheumatism Centre. It was therefore particularly desirable to compare this observer's gradings with those of his clinical and radiological colleagues, and the material has been analysed mainly from this point of view.

Results

Therapeutic Trial.—In this study 192 hand films from sixty patients with early rheumatoid arthritis were read independently by six different observers. The total scores (Table I) show that there are considerable discrepancies. The radiologists recorded more films as normal, while the clinicians recorded more films as abnormal and tended more often to rate these changes as moderate or severe in degree, particularly as regards porosis. This last discrepancy may be partly due to the radiologists' greater awareness of the technical causes of apparent porosis.

In recording erosions, the main differences appear to be due to language—thus Observer IV graded erosions as moderate or severe in 53 instances, whereas Observer V graded erosions as moderate in only thirteen instances and severe in none. On the other hand, the total number of films considered abnormal on account of erosions varies less, the range being from 81 for Observer V to 105 for Observer III.

In recording porosis, the differences are even greater and are not reduced by combining all grades of abnormality. The total number of films considered abnormal on account of porosis range from 153 for Observer IV to 59 for Observer V.

These films were taken by various techniques and only a proportion of them included a control bone to facilitate estimates of porosis, but separate consideration of the gradings of the 55 films with control bones showed practically as much disagreement; the assessment of porosis was exceptionally difficult in many of these films owing to great variations in radiographic technique.

The differences of opinion over the assessment of porosis in individual films were also very great, as illustrated in Table II where Observers IV and V, the two who disagree most, are compared.

TABLE II
THERAPEUTIC TRIAL—POROSIS

Observer IV \ Observer V	0	1	2	3	4	Total
4	—	2	8	3	2	15
3	10	31	37	3	—	81
2	29	22	6	—	—	57
1	18	3	—	—	—	21
0	15	3	—	—	—	18
Total	72	61	51	6	2	192

It will be noted that disagreement of three grades occurred in 12 and of two grades in 68 of the 192 films. It is therefore apparent that recording estimates of porosis based upon inspection of films can be of only limited value.

TABLE I
THERAPEUTIC TRIAL

Sign	Grade	Observers					
		Clinicians				Radiologists	
		I	II	III	IV	V	VI
Erosion	0 = None	62	50	39	49	59	56
	1 = Doubtful	41	50	48	39	52	50
	2 = Slight	51	43	53	51	68	57
	3 = Moderate	32	36	47	45	13	25
	4 = Severe	6	13	5	8	0	4
	Total Abnormal	89	92	105	104	81	86
Porosis	0 = None	30	34	28	18	72	85
	1 = Doubtful	45	77	73	21	61	29
	2 = Slight	75	56	60	57	51	50
	3 = Moderate	32	21	28	81	6	23
	4 = Severe	10	4	3	15	2	5
	Total Abnormal	117	81	91	153	59	78

The differences of opinion over the assessment of erosion in individual films is illustrated in Tables III to V, in which are compared the readings of Observers V and VI (the two radiologists), Observers III and V (the pair with greatest differences), and Observers II and IV (two typical clinicians).

TABLE III

THERAPEUTIC TRIAL—EROSION

Observer V

Observer VI	0	1	2	3	4	Total
4	—	—	1	3	—	4
3	—	1	19	5	—	25
2	1	16	36	4	—	57
1	17	20	12	1	—	50
0	41	15	—	—	—	56
Total	59	52	68	13	0	192

TABLE IV

THERAPEUTIC TRIAL—EROSION

Observer V

Observer III	0	1	2	3	4	Total
4	—	—	—	5	—	5
3	—	1	39	7	—	47
2	2	22	28	1	—	53
1	22	25	1	—	—	48
0	35	4	—	—	—	39
Total	59	52	68	13	0	192

TABLE V

THERAPEUTIC TRIAL—EROSION

Observer IV

Observer II	0	1	2	3	4	Total
4	—	—	—	6	7	13
3	—	—	8	27	1	36
2	2	4	28	9	—	43
1	15	19	13	3	—	50
0	32	16	2	—	—	50
Total	49	39	51	45	8	192

Although it will be seen that the distribution as shown in the Tables is not strictly normal, it is considered that the deviation is not so great as to preclude the use of correlation coefficients in analysis of the data. The results for the three pairs of observers illustrated are as follows:

Observers V and VI: $r = +0{\cdot}77$ (Table III)
Observers III and V: $r = +0{\cdot}86$ (Table IV)
Observers II and IV: $r = +0{\cdot}83$ (Table V)

Observer I had had more experience of grading rheumatoid changes in hand films than the other observers, since he had been reading films from field surveys for over 2 years, and it is interesting to note that his total scores for erosion (Table I) fell very near the mean of the other five observers.

This observer's readings of individual films were compared with a composite score of the other five observers, obtained by adding together the individual scores of each film recorded by these observers and dividing the total by 5. The result is shown in Table VI. Here the correlation is: $r = +0{\cdot}91$.

TABLE VI

THERAPEUTIC TRIAL—EROSION

Observer I

Average of Observers II to VI	0	1	2	3	4	Total
4	—	—	—	—	—	0
3·8	—	—	—	—	3	3
3·6	—	—	—	—	2	2
3·4	—	—	—	—	—	0
3·2	—	—	—	2	—	2
3	—	—	—	8	1	9
2·8	—	—	1	7	—	8
2·6	—	—	10	4	—	14
2·4	—	—	5	7	—	12
2·2	—	3	7	3	—	13
2	—	—	10	1	—	11
1·8	—	4	7	—	—	11
1·6	—	3	5	—	—	8
1·4	1	3	1	—	—	5
1·2	4	5	1	—	—	10
1	2	7	2	—	—	11
0·8	4	7	1	—	—	12
0·6	8	4	1	—	—	13
0·4	12	3	—	—	—	15
0·2	18	2	—	—	—	20
0	13	—	—	—	—	13
Total	62	41	51	32	6	192

The individual readings of the other observers have been similarly compared with the composite scores of their colleagues, the results being as follows:

Observer II: $r = +0{\cdot}88$;
Observer III: $r = +0{\cdot}88$;
Observer IV: $r = +0{\cdot}87$;
Observer V: $r = +0{\cdot}89$;
Observer VI: $r = +0{\cdot}83$.

There is thus no great difference between the performance of the various observers.

The same 192 films were re-read by Observer I using a single unified grading for rheumatoid changes instead of the separate gradings for porosis and erosion. The results are shown in Table VII.

TABLE VII
THERAPEUTIC TRIAL

Grade	Erosion	Porosis	Rheumatoid Arthritis
0 = None ..	62	30	55
1 = Doubtful ..	41	45	36
2 = Slight ..	51	75	65
3 = Moderate ..	32	32	29
4 = Severe ..	6	10	7
Total Abnormal ..	89	117	101

In comparing individual films the following results were obtained:

Rheumatoid arthritis and Erosion: $r = +0{\cdot}82$;
Rheumatoid arthritis and Porosis: $r = +0{\cdot}72$;
Rheumatoid arthritis and a combined factor of $\frac{\text{Erosion} + \text{Porosis}}{2}$: $r = +0{\cdot}88$.

Thus, although porosis is difficult to estimate and may be unreliable, it has played a considerable part in the overall diagnosis of rheumatoid arthritis by Observer I in this sample of films.

Leigh Survey.—The 126 films of the hands in this series were all taken by the same technique and nearly all included a control bone. Unlike the first set of films, they were obtained from a population sample in the 55-64 age group which included very few individuals with early active rheumatoid arthritis. A substantial number, however, had old or inactive rheumatoid arthritis, many had advanced osteo-arthritic changes, and quite a number of the women also had osteoporosis due to conditions other than rheumatoid arthritis.

These 126 films were read by Observer I on three occasions, the first and third readings being done jointly with an additional clinician (Observer VII). In the first and second readings only the combined grading for rheumatoid arthritis was recorded, but in the third reading porosis and erosions were graded separately and recorded irrespective of the apparent cause of these changes. The findings are shown in Table VIII, together with a composite score obtained by adding the individual gradings of the first two readings to the score for erosion and/or porosis, whichever was the highest, and dividing the total by 3.

Comparison of the gradings of the individual films in the first and second reading is shown in Table IX. The gradings were reasonably reproducible: $r = +0{\cdot}80$. More films were recorded as normal or doubtful by the one observer reading alone, but in no instance did the single observer grade a film as abnormal that had been considered normal or doubtful in the first reading.

TABLE IX
LEIGH SURVEY—RHEUMATOID ARTHRITIS

First Reading

Second Reading	0	1	2	3	4	Total
4	—	—	—	1	4	5
3	—	—	—	1	—	1
2	—	—	16	—	—	16
1	4	20	5	—	—	29
0	44	25	6	—	—	75
Total	48	45	27	2	4	126

Comparison of the rheumatoid gradings with those for porosis showed wide disagreement: $r = +0{\cdot}34$ for the first and $+0{\cdot}36$ for the second rheumatoid arthritis reading. This disagreement is

TABLE VIII
LEIGH SURVEY

Grade	Rheumatoid Arthritis		Third Reading		Composite Score	
	First Reading	Second Reading	Porosis	Erosion		
0 = None	48	75	84	74	0–$\frac{1}{3}$	53
1 = Doubtful	45	29	24	28	$\frac{2}{3}$–$1\frac{1}{3}$	48
2 = Slight	27	16	15	17	$1\frac{2}{3}$–$2\frac{1}{3}$	19
3 = Moderate	2	1	1	3	$2\frac{2}{3}$–$3\frac{1}{3}$	1
4 = Severe	4	5	2	4	$3\frac{2}{3}$–4	5
Total Abnormal	33	22	18	24	$\geqslant 1\frac{2}{3}$	25

largely due to the almost complete absence of porosis in the 41 films from males in this series. In females the total distribution of the various grades of porosis and of rheumatoid arthritis hardly differ, but, even so, the correlation in females between porosis and the first and second rheumatoid arthritis readings is not more than +0·54 and +0·58. Comparison of the rheumatoid gradings with those of erosion, on the other hand, showed good agreement: r for the two sexes combined = +0·81 and +0·84, with no conspicuous difference between males and females.

Osteoporosis as seen in hand films is not always qualitatively the same. Thus, in old age and the post-menopausal state the porosis develops slowly over many years and the radiological appearance is one of thin and sparse trabeculation in the bone, the trabecular pattern being, if anything, more clearly defined than usual. In active early rheumatoid arthritis and in post-traumatic porosis, the bone is more rapidly removed over a period of weeks and months and the radiological appearances differ. Thus, the trabecular pattern as seen in hand films is "smudged" and "blurred" with spotty areas of translucency.

This appearance can to some extent be recognized irrespective of estimates of total bone density. Amongst the films obtained from the sample population aged 55-64 years were six showing porosis of the more chronic type and one showing acute porosis associated with a Colles fracture. These were not considered as evidence of rheumatoid arthritis and this accounts for the poor correlation between osteoporosis and radiological rheumatoid arthritis in this group.

The remaining 254 films from the Leigh Survey which were not considered to show any definite signs of rheumatoid arthritis on the first reading were read a second time, porosis and erosions being recorded separately irrespective of whether these changes were thought to be due to rheumatoid arthritis or not.

Minimal porosis was recorded in films from two men and fourteen women, and moderate porosis in films from three women.

Minimal erosions were recorded in films from three men and three women.

In only one film did porosis and erosions coincide, and this was the only film in which the changes might on re-reading have been considered to be due to rheumatoid arthritis. The porosis in the others was all of the chronic variety. Finally, six minimal erosions were associated with definite evidence of trauma or deformities to which they were thought to be related.

South Wales Survey.—The results of the two separate readings of these 259 hand films by Observer I are shown in Table X. Between the first and second reading there was an interval of over one year, and during that time most of the other studies reported here had been carried out. As a result, this observer's criteria for the radiological grading of rheumatoid arthritis had become stricter. This can be seen by the uniform shift in the diagram and by the fact that 27 films that were graded as positive on the first reading were graded as negative or doubtful on the second; whereas no films were graded as positive on the second reading which were considered negative or doubtful on the first. The correlation between first and second readings is in general good: r = +0·88.

TABLE X

SOUTH WALES SURVEY—RHEUMATOID ARTHRITIS

First Reading

Second Reading	Total	128	40	44	22	25	259
4		—	—	—	—	17	17
3		—	—	—	16	7	23
2		—	—	17	5	1	23
1		11	12	16	1	—	40
0		117	28	11	—	—	156
	Score	0	1	2	3	4	Total

Conclusions

(1) Osteoporosis may be difficult to assess and there can be wide disagreement between different observers in recording even its presence or absence.

(2) Erosion can be recognized with reasonable certainty, and fair agreement is obtained in recording the presence or absence of this change, but there is wide disagreement over degree of severity. This is presumably a language difficulty and might be partly overcome by the use of standard films.

(3) In films from field surveys there is little correlation between erosions and porosis, because of the prevalence of non-rheumatoid porosis in older age groups. Erosions should therefore be mainly relied upon for grading survey films for rheumatoid arthritis.

(4) The x-ray recordings of Observer I are about average and are not likely to differ greatly from

the mean readings obtained from a number of clinicians and radiologists.

(5) In grading films for rheumatoid arthritis there is a lack of reproducibility, especially at the important division between doubtful and slight so that in survey work a composite score derived from several separate readings should be used.

(6) As criteria for diagnosis may differ between observers and may change with time, particularly at the division between doubtful and slight, some agreed set of standard reference films should be employed if *x*-ray changes are to be used for assessing comparative prevalence rates of rheumatoid arthritis by different observers, or by the same observer at different times.

(7) If *x*-rays of the hands are used to assess progress in therapeutic trials, it is essential that all films be read by the same observer, preferably at a single session.

Summary

Three sets of *x* rays of the hands have been used to estimate the degree of inter-observer and intra-observer differences in interpreting changes of rheumatoid arthritis.

Wide disagreement between observers was found in the assessment and even in the recognition of osteoporosis. Erosion was recognized with reasonable certainty, but its severity was variously interpreted.

The reassessment, after a year, of a set of 259 films by the same observer showed a small difference between the two readings; this difference was due to stricter criteria for the radiological grading of rheumatoid arthritis at the second reading.

Suggestions are made to ensure a greater uniformity in grading *x* rays in field surveys and therapeutic trials, such as an agreed set of standard reference films and the reading of all films by the same observer, preferably at a single session.

The films of the therapeutic trial were read by Drs. E. G. L. Bywaters, J. J. R. Duthie, D. E. Fletcher, K. A. Rowley, and H. F. West. Without their co-operation and helpful criticism this study would not have been possible and I am deeply indebted to them for their help. I should also like to thank Dr. W. E. Miall of the Pneumoconiosis Research Unit for providing the films of the South Wales Survey.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.

Cochrane, A. L., Campbell, H. W., and Stein, S. C. (1949). *Amer. J. Roentgenol.*, **61**, 153.

——, and Garland, L. H. (1952). *Lancet*, **2**, 505.

Empire Rheumatism Council (1955). *Annals of the Rheumatic Diseases*, **14**, 353.

Fletcher, C. M., and Oldham, P. D. (1949). *Brit. J. industr. Med.*, **6**, 168.

Fletcher, D. E., and Rowley, K. A. (1952). *Brit. J. Radiol.*, 25, 282.

Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Diseases (1954). *Brit. med. J.*, **1**, 1223.

—— (1955). *Ibid.*, **2**, 695.

Miall, W. E. (1955). *Annals of the Rheumatic Diseases*, **14**, 150.

——, Caplan, A., Cochrane, A. L., Kilpatrick, G. S., and Oldham, P. D. (1953). *Brit. med. J.*, **2**, 1231.

Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 1.

Steven, G. D. (1947). *Annals of the Rheumatic Diseases*, **6**, 1, 184.

Yerushalmy, J., Garland, L. H., Harkness, J. T., Hinshaw, H. C., Miller, E. R., Shipman, S. J., and Zwerling, H. B. (1951). *Amer. Rev. Tuberc.*, **64**, 225.

——, Harkness, J. T., Cope, J. H., and Kennedy, B. R. (1950). *Ibid.*, **61**, 443.

Signes radiologiques de l'arthrite rhumatismale. Une étude des différences d'interprétation des radiologies des mains selon l'observateur

Résumé

A l'aide de trois séries des radiographies des mains on détermina l'amplitude des divergences entre plusieurs observateurs et chez le même observateur dans l'interprétation des lésions rhumatismales.

On trouva un désaccord considérable entre les observateurs en ce qui concerne l'évaluation et même la présence de l'ostéoporose. Le diagnostic de l'érosion fut plus facile, mais sa sévérité fut variablement interprétée.

Une seconde évaluation par le même observateur un an plus tard d'une série de 259 clichés révéla quelques différences dues au fait que ses critères pour l'appréciation radiologique de l'arthrite rhumatismale devinrent plus rigoureux.

Pour assurer une appréciation plus uniforme des radiologies au cours des enquêtes "de champ" et des essais thérapeutiques, on suggère quelques remèdes, tels qu'une série convenue de clichés-étalon et l'interprétation de tous les clichés par le même observateur, préférablement au cours d'une seule session.

Manifestaciones radiológicas de la artritis reumatoide. Un estudio de las diferencias entre observadores en la interpretación de la radiografías de manos

Sumario

Con la ayuda de tres series de radiografías de manos se determinó la amplitud de las diferencias entre varios observadores y en el mismo observador respecto a la interpretación de las lesiones reumáticas.

Un desacuerdo considerable entre varios observadores fué revelado en la valoración y hasta en la afirmación de la presencia de la osteoporosis. El diagnóstico de la erosión fué más facil pero hubo mayores variaciones en la interpretación de su severidad.

La valoración repetida por el mismo observador un año después de 259 clisés resultó en pequeñas diferencias, debidas al hecho de que los criterios en la apreciación radiológica de la artritis reumatoide fueron más rigorosos la secunda vez.

Para asegurar la valoración más uniforme de radiologías durante investigaciones "de campo" y ensayos terapéuticos, se sugieren algunos remedios, tales como una serie convenida de clisés de norma y la interpretación de todos los clisés por el mismo observador, preferablemente en el curso de una sesión.

Ann. rheum. Dis. (1955), **15**, 61.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE SECOND INTERIM SCIENTIFIC SESSION

December, 1955

Dr. Charles L. Short, President of the American Rheumatism Association, took the chair at the opening meeting of the second interim scientific session held on December 9, 1955, at the Clinical Center, National Institutes of Health, Bethesda, Maryland. He thanked those who had arranged the scientific programme and social events, and Dr. J. A. Shannon, Director of the National Institutes of Health, welcomed the members of the American Rheumatism Association and their guests.

Abstracts of eighteen papers and the discussions thereon are printed below, together with the titles of 23 papers presented but not read.

Uric Acid Formation in Patients with Gout. The Incorporation of 4-Amino-5-Imidazolecarboxamide-C^{13} into Uric Acid. By J. E. SEEGMILLER, LEONARD LASTER, and DEWITT STETTEN, JR., *Bethesda, Md.*

By studying the incorporation of glycine-N^{15} into uric acid, Benedict and others (1952, 1953) have shown that some gouty patients appear to possess a "shunt mechanism" for urate biosynthesis. Because animal and bacterial systems incorporate 4-amino-5-imidazolecarboxamide, "AIC", into purines at a stage of the biosynthetic chain between glycine and uric acid, AIC was synthesized with C^{13} in the four position and was fed to human subjects in order to learn more about the chemical reactions involved in the proposed "shunt mechanism".

When 14 mg. per kilo AIC-C^{13} was fed to two normal males, 23 per cent. was incorporated into urinary uric acid and 20 per cent. was recovered unchanged in the urine without significant isotope dilution (Seegmiller and others, 1955). From the results it was concluded that AIC is incorporated into uric acid promptly, but there is an additional contribution of isotope to uric acid from a body pool with a slow turnover rate, presumed to arise largely from tissue purines. A pool of free AIC in the body was not detected. Glycine-N^{15} was fed with the AIC and, in the dosage level used, AIC appeared capable of inhibiting the *de novo* synthesis of uric acid from glycine.

Similar studies have been performed on patients with gout who belong to the class showing normal incorporation of N^{15} into uric acid. Although there is some suggestion of an increased total incorporation of AIC into uric acid in these patients, our data also shows many points of similarity to the pattern of incorporation seen in the normal. AIC exerts a depressant effect on the *de novo* synthesis of uric acid from glycine in gouty patients so far studied, as well as in normal subjects.

Discussion.—DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): I wonder if this discovery that uric acid formation is decreased may have a clinical application? Shall we be able to use this material in the treatment of gouty patients who may be forming uric acid excessively?

DR. SEEGMILLER: It is very unlikely that it would have a use in treatment. We found in the 2 days following the administration of this dose of AIC that 200 g. extra uric acid was excreted in the urine, which resulted, presumably, from this very direct and rapid conversion of AIC to uric acid.

The possibility of alleviating an acute attack of gout by suppressing uric acid precursors has, of course, occurred to us, and we have tried it in a few cases, but without any real definitive results.

DR. L. MAXWELL LOCKIE (*Buffalo, N.Y.*): Has Dr. Seegmiller performed any determinations on these possible precursors in which some of the AIC may be present? This would be of great interest to those of us who are concerned with fundamental studies of uric acid metabolism. This presentation of factual evidence represents a tremendous amount of time and effort, and it is nice to have more body pool determinations reported.

DR. SEEGMILLER: No, we have not attempted yet to isolate and characterize any metabolic products of AIC other than the uric acid.

REFERENCES

Benedict, J. D., Roche, M., Yü, T. F., Bien, E. J., Gutman, A. B., and Stetten, D., Jr. (1952). *Metabolism*, 1, 3.
——, Yü, T. F., Bien, E. J., Gutman, A. B., and Stetten, D., Jr. (1953). *J. clin. Invest.*, 32, 775.
Seegmiller, J. E., Laster, L., Stetten, D., Jr. (1955). *J. biol. Chem.*, 216, 653.

Pathological Study of the Renal Lesions found in 27 Patients with Gout. By JOHN G. MAYNE, *Rochester, Minn.*

Inasmuch as urate diuresis is a basis of the modern therapy of gout, renal disease in patients with gout is of serious import. The kidneys of 27 patients with gout were studied at necropsy to determine the frequency and type of renal lesions present.

Fourteen patients had had symptoms or signs of gout for less than 10 years; thirteen patients had had such evidence for 11 or more years.

In these 27 patients, renal disease was the major cause of death before the age of 40. Six patients died in uraemia of renal disease, eight died of various types of heart disease, five of neoplasms, and eight of other causes.

The kidneys of eight patients were essentially normal and contained no urate deposits by gross or microscopic observation. Eight patients had small kidneys, and eight had atrophic kidneys. In three cases pathological details were incomplete. Urate deposits were found in seventeen of these nineteen cases (63 per cent. of the total).

Urate deposits and those tissue alterations produced by them were the only lesions pathognomonic of gout. The intra- or extra-tubular location of the urate deposits could not be satisfactorily determined by histological study alone. Vascular lesions other than those found in five cases of glomerulonephritis, one of chronic pyelonephritis, and three of essential hypertension were compatible with the age group comprising the series.

The relative frequency of the lesions of glomerulonephritis was not explained.

Discussion.—DR. LEONARD LASTER (*Bethesda, Md*): Were any of these patients receiving Benemid for long periods of time? If so, did the ones who received Benemid show fewer deposits of urate in their kidneys?

DR. MAYNE: None of the patients in this study had had Benemid.

DR. JOHN N. SWANSON (*Toronto, Ont., Canada*): I have been studying 176 patients with gout, of whom 38 had clinical or laboratory evidence of kidney function impairment. Eight of these came to autopsy, and four had urate deposits, similar to those you have mentioned, while three apparently had chronic glomerulonephritis.

One, however, had congenital hypoplasia of the left kidney and was particularly interesting as this may be of aetiological significance. The patient concerned had been a French-Canadian, and I do not believe gout is a very common disease in his race. He was one of fifteen children, and there was no family history of gout amongst them, or any other relatives as far as was known. During the recent war he was wounded in the abdomen, and in the subsequent hospitalization it was noticed that his left kidney was not functioning. It was thought at first that the bullet had severed his left ureter. He subsequently developed pyelonephritis in the remaining kidney and, during the last 3 or 4 years of his life, had frequent attacks of gouty arthritis. At autopsy it was discovered that the left kidney was hypoplastic, and only a few mesonephrons were seen microscopically. It is surely more than just coincidence that gout developed in this man who had one kidney absent, and the other diseased, when his race has gout but infrequently, and the rest of his family was free from gout.

DR. MAYNE: I think that is a most interesting study. The one case of chronic pyelonephritis which I mentioned had occurred in a man who had a single kidney, congenitally. He had been troubled with recurring attacks of ureteral obstruction from the age of 15 or 18. He had been repeatedly cystoscoped during his lifetime. This I think is an interesting comparison with your French-Canadian patient.

DR. JOSEPH J. BUNIM (*Bethesda, Md*): I wonder if, in retrospect, Dr. Mayne could distinguish by clinical and laboratory evidence the tubular lesions from the kidneys in gouty patients which show vascular or glomerular lesions.

I think about 3 years ago Dr. Modern and his associates of California reported that they could segregate the lesions which were isolated or confined to tubular changes and were not associated with glomerular or vascular changes. They believed that these might be recognized clinically by a dissociation of certain laboratory and clinical features. For example, such patients had impairment of renal function, low excretion of dye, hyposthenuria, and low clearance, but hypertension, albuminuria, and a significant amount of cylindruria were absent. Such patients, they felt, had a much better prognosis than gouty patients with non-specific glomerular or vascular lesions.

DR. MAYNE: That is most interesting. In my series renal function studies using a dye retention (*i.e.* PSP, and so forth) were not reported, so I cannot answer that part of the question.

The tubular lesions did seem to be associated primarily with patients who had other forms of renal disease. Thus, in the five cases of glomerulonephritis, all but one patient showed evidences of tubular lesions with urate deposits; in the three cases of nephrosclerosis, all had tubular lesions with urate deposits.

There were a number of other patients who had urate deposits in the tubules. These had no sign of other than a minimal arterio- or arteriolo-sclerosis which usually seemed compatible with their ages which were all in the 60s and 70s, except one man who was 90.

Rheumatoid Disease in Swine. By G. M. NEHER, L. P. DOYLE, C. B. SWENSON, and DENNIS SIKES, *Lafayette, Ind., and Athens, Ga.*

Since rheumatoid disease was the primary cause for the condemnation of swine carcasses in 1954, it is one of the major problems in animal health to-day. The disease in swine shows many similarities to rheumatoid arthritis in the human being, and it is conceivable that experimentation with swine may facilitate a better understanding of the corresponding disease in man.

The symptoms of arthritis in swine are swollen painful joints accompanied by severe lameness with apparent muscular soreness. The pathological changes in the joints are essentially proliferative and non-suppurative with numerous foci of lymphocytes. Granulomatous proliferations of the synovial capsule and villi occur with pannus formation, destruction of the articulating cartilage and subchondral cellular reactions. Intra-articular fibrous adhesions are a common feature.

Radiographically, a narrowing of the joint spaces and osteophyte formations can be observed from the third to fourth month. This is followed by some rarefaction of adjacent bone and massive exostoses which may result in ankylosis of the joints. The authors frequently failed to isolate organisms from the affected joints 6 months after exposure even though the arthritic process continued unabated.

Arthritis occurs naturally on farms as a chronic manifestation of swine erysipelas which is an acute and infectious disease caused by the bacterium *Erysipelothrix*

rhusiopathiae. Using 191 swine, the authors were able to reproduce the disease with this organism by seven different exposure procedures. 35 per cent. of the animals died of the acute disease and 40 per cent. of the survivors developed chronic arthritis. When 95 animals were vaccinated and subsequently challenged, marked anaphylactic-type shock reactions were evident. The death rate due to the acute form of the disease was markedly reduced, but arthritis developed in between 90 and 100 per cent. of cases. These findings strongly suggest the possibility that sensitization is an important factor in the aetiology of the disease.

Swine with advanced rheumatoid disease respond very well to cortisone therapy; ACTH seems more beneficial in early cases.

Discussion.—DR. MORRIS SPIELBERG (*Brooklyn, N.Y.*): Did any of these swine become pregnant and, if so, did it in any way change the progress of the type of response?

DR. NEHER: We have made some attempts to breed from arthritic sows, but these attempts have failed. Females with advanced rheumatoid disease usually fail to exhibit any of the overt signs of oestrus and it is probable that they are not having regular ovarian cycles. None of the swine in the experiment reported here became pregnant.

DR. RALPH J. WEDGWOOD (*Cleveland, Ohio*): First, is there any hereditary nature to the disease; and, secondly, is there any record of age at onset, and does it bear any relationship to what we call puberty in man?

DR. NEHER: There seems to be no hereditary indication in this particular disease. To the casual observer there might seem to be, since droves of swine on different farms show marked variations in the degrees of immunity. The bacterium *Erysipelothrix rhusiopathiae* is very widespread in nature, and the variations in the different families of swine quite possibly reflect only the difference in the amount of immunity acquired following clinical or subclinical experiences with the organism. We had considerable difficulty in locating a drove of swine in which the disease had not occurred since the herd was established 12 years previously, so it was difficult to obtain susceptible swine.

In answer to your second question, there does seem to be an age relationship. Ordinarily young animals up to 3 months of age do not develop this type of rheumatoid disease. I have seen it on occasion but it is extremely rare. In animals over 3 months of age the disease is much more prevalent, and in fact domesticated swine begin to reach puberty at about 3 months of age.

DR. OSCAR SWINEFORD (*Charlottesville, Va*): Did you attempt to desensitize these animals? Is this organism pathogenic in animals other than swine?

DR. NEHER: We did not attempt to desensitize the animals other than by allowing them to go untreated for a period of time.

So far as the pathogenicity of *E. rhusiopathiae* to other animals is concerned, it is highly pathogenic in such laboratory animals as mice and pigeons, and these two species are used frequently in identifying the organism. *Erysipelothrix rhusiopathiae* has been isolated from arthritic lambs and calves, but the arthritis produced in these animals does not seem to progress to the true rheumatoid type.

The organism has also been isolated from goats, horses, chickens, turkeys, and man.

DR. MORRIS A. BOWIE (*Bryn Mawr, Pa*): I should like to congratulate Dr. Neher and colleagues for bringing into sharp focus this problem which has intrigued people working in the rheumatic field for a long time. A number of years ago when Dr. Rosenthal and I were trying to elucidate some of the factors involved in the degeneration of cartilage, it became apparent that the most marked changes seen in abattoir material were in joints of the fore extremity, regardless of the age of the animal from which the material was selected. We reasoned that the prominence of the degenerative changes in the forelimbs was due to the fact that cattle usually rise from the ground using their forelimbs. Did most of the material which you showed come from the forelimbs of hogs?

Also, what is the normal life span of the average pig? I was impressed by the high incidence of osteophyte formation within a short period in the spine and what seemed to be the apparent disappearance of the pannus after an appreciable period. Certainly this most interesting study deserves further investigation.

DR. NEHER: In so far as the life span of a hog is concerned, here we have, as you can recognize, a rather curious situation. Ordinarily swine are sent to market at about 6 to 7 months of age, at which time they weigh between 200 and 240 lb., depending upon how good the farm management has been.

I think that swine about 6 to 7 years old would be considered to approach senility. Ordinarily, under farm conditions, the animals are not kept this long, and we very rarely if ever see swine of this age. Animals that are kept past the marketing age are used for breeding. After sows have farrowed four or five litters (two litters being born each year), in many instances they become careless mothers, develop lactation difficulties, or have litters of reduced size, and are subsequently sold for slaughter. Consequently at our veterinary department we very rarely see swine which are over 5 years of age.

DR. ANTOINETTE POPOVICI (*Washington, D.C.*): What is the sex ratio in rheumatic disorders in swine? Have you found any relationship between the incidence of this disease and obesity in swine or any correlation between the accumulation of adipose tissue and the degree of rheumatic involvement?

DR. NEHER: Through selective breeding for many years swine have been evolved which yield carcasses with a high fat content. The average back-fat thickness over the carcass of a butchered hog may well be in the neighbourhood of 1½ to 2 in., so that one might say that swine in general are quite obese animals.

Our experiments were not designed to study the relationship of obesity to the incidence of acute swine erysipelas or arthritis. The animals used were about the same size and age and carried roughly the same degree of what livestock people call conditioning or fat over the body. Consequently our experimental evidence will not afford a precise answer to your question, but it is generally believed that fat swine are more susceptible to acute swine erysipelas than leaner swine of the same age. The body temperature in this disease will frequently rise to 108 and even 109° F., and since more obese animals have greater difficulty in dissipating body heat the course of the disease is usually more acute and the mortality higher. The normal temperature in a pig will vary quite markedly between 100·4 and 104° F. One cannot say that the incidence of rheumatoid arthritis in swine is greater in obese animals, since a loss of body weight and general

inanition occurs concomitantly with the progress of the disease.

There seems to be no sex difference in this disease. The 191 animals reported on to-day were roughly half females and half barrows. A barrow is a male which has been castrated prior to puberty; swine producers routinely follow this practice except when certain animals are saved for breeding purposes. We have examined a few boars with naturally occurring rheumatoid disease, but not enough to establish whether or not sex differences are present.

DR. MORRIS ZIFF (*New York, N.Y.*): Have you cultured the chronic tissue lesions for *Erysipelothrix rhusiopathiae*?

DR. NEHER: After we challenge these animals intravenously and they have the acute disease, we can isolate *E. rhusiopathiae* from all the parenchymatous tissues until after the fever subsides. Then we are able to isolate the organism quite routinely from the regional lymph nodes which drain the limbs where joint involvement has taken place, as well as from the affected joints.

However, isolation of the organism from the joints of chronic cases of over 6 months' duration is extremely difficult. We rarely isolate the organism after this time, although the proliferative changes in the joints may be by no means advanced at that time. Thus, it would seem that rheumatoid disease progresses unabated in the absence of the micro-organism.

DR. MORRIS ZIFF: Is chronic arthritis in association with *E. rhusiopathiae* infection ever seen in man? I know the acute disease will produce arthritis, but that is pyogenic. Do you know whether a chronic sterile polyarthritis is ever seen in man?

DR. NEHER: In man, *E. rhusiopathiae* causes a skin lesion called an erysipeloid. It is my impression that no experimental evidence is available which would incriminate this bacterium as an aetiological factor in arthritis in man.

DR. MORRIS ZIFF: Septic arthritis has been reported, but it is important to know whether any of the septic cases ever go on to chronic arthritis.

I asked Dr. Neher for samples of serum from infected swine and received from him eighteen sera which we tried to absorb to do the sheep agglutination test. There was a lot of heterophil antibody in the sera and we were able to absorb only nine sera successfully. We tested these nine, three of which were from controls and six from arthritic swine. The three controls gave completely negative results. Of the six from arthritic swine, four showed agglutination in a titre of 1 in 14. This is a borderline titre, but in human sera we should regard them as positive.

I do not know the significance of the sheep cell agglutination test in swine, or whether this observation is repeatable, and I do not know whether a raised heterophil antibody titre would invalidate the results, but the results are suggestive.

DR. NEHER: I am very pleased to hear these results, and I shall be happy to draw more blood samples and send them to Dr. Ziff for further experiments.

DR. CHARLEY J. SMYTH (*Denver, Colo.*): Our veterinarian friends have again called our attention to a disease in swine which in some respects resembles rheumatoid arthritis in man. In Michigan in 1939 and 1940 we became interested in trying to find an experimental animal that might be suitable to study as a counterpart to man, and we were fortunate in obtaining about 150 hogs from one of the abattoirs in Detroit. We studied these sections microscopically and found changes that are not dissimilar to those that have been described to-day; but on reviewing them with the chief of our pathology department at that time, we were assured that this was primarily a suppurative disease and, with the knowledge that erysipelas is a common illness in swine, we felt that the proliferative changes were probably an irritative phenomenon in a previously damaged joint, which was not comparable to the disease which we call rheumatoid arthritis in man.

I think it would be interesting, in view of these recent studies, to study the carcases of these animals for vascular lesions, peripheral nerve lesions, subcutaneous nodules, and evidence of myocytic lesions which might support the idea that this disease is related to the human disease.

The term "rheumatoid" should not be used without great care in translating this data into human data.

DR. IRVIN STEIN (*Philadelphia, Pa*): You obtained a high degree of arthritis on intra-articular injection. Was that a local reaction or did the arthritis appear in other joints as well?

DR. NEHER: We did produce the disease in other joints, and the incidence of rheumatoid lesions in other joints seemed to be as great as in the injected joints. In some cases the acute inflammation would subside in the injected joints, and the disease would become localized in other joints, indicating that we had set up a septicaemia in the animal by this particular route of exposure.

DR. RICHARD T. SMITH (*Philadelphia, Pa*): I have had the opportunity of following this study for 3 or 4 years. Dr. Neher and his colleagues should be congratulated on their hard work. You cannot imagine what is required in order to develop chronic arthritis in pigs, since so many of them die simply because they will not stand on their painful joints. These men were dedicated to their task to such an extent that every morning they went down to the pens, grasped the pigs by the ears and hauled them up on their front feet, and by the tail and hauled them up on their hind feet, so that they would eat. That is the way to prevent starvation and preserve the life of the pig until the chronic changes have had time to develop.

The acute changes which have been seen previously and were not considered to be too closely allied to rheumatoid arthritis present a different picture as time goes on. *X* rays show evident calcification of the synovial membrane, which occurs rapidly in the pigs since they will not move a painful joint. This permits ankylosis to develop rapidly provided they live long enough.

A great deal more work was done than has actually been reported, and there are other findings that are comparable to and parallel with human rheumatoid arthritis. In the pig the *Erysipelothrix* disappears, the arthritis progresses, and the similarity to human arthritis becomes more marked.

DR. JOHN H. VAUGHAN (*Richmond, Va*): Have you been able to induce this disease with dead organisms, both at the time of vaccination and in challenge?

DR. NEHER: We have experiments under way at present in which 36 animals are involved, and we are attempting to produce rheumatoid disease in the absence

of living organisms. All I can say at this time is that several necropsies have been performed and the results appear encouraging, but it will be another month or two before I can make a more definite statement than that. We may be on the right track in producing the condition in the absence of a living organism, but it also seems that we have to use at least the killed organism. There are certain antigenic properties in the organism itself whether living or dead, which seem to be necessary aetiological factors in the disease.

DR. SAMUEL BACHRACH (*Worcester, Mass.*): Have you tried any other substances in an attempt to produce this disease in swine other than those you have mentioned?

DR. NEHER: We have not made any serious attempts to produce the disease with micro-organisms other than *E. rhusiopathiae*, chiefly because we had succeeded in producing a rheumatoid disease, resembling the naturally occurring disease in every respect, with this organism. We have examined the joints of several hundred field cases and, with very few exceptions, when the organism isolated from the joints was *E. rhusiopathiae*.

In cases of suppurative arthritis, which are quite rare in older swine, we have no difficulty in isolating pyogenic bacteria, usually streptococci and less frequently staphylococci. Although this type of arthritis is quite common in pigs several weeks old, it is probably not associated with the true rheumatoid disease of swine which usually occurs in animals over 3 months of age. When the rheumatoid changes are advanced we do not isolate organisms routinely.

DR. CHARLES RAGAN (*New York, N.Y.*): Dr. Stoerk at the Merck Institute has produced an arthritis in rats, with Freund's adjuvant and homologous lymphoid tissue, which has many similarities to that described by Dr. Neher in swine. There are, however, no remissions and no exacerbations after an initial period of 2 months. Is this also true in the swine arthritis? If so, I think it would fall into the same category as that described by Dr. Smyth: this is one insult which is not sustained over a period of years as is the case with rheumatoid arthritis.

DR. NEHER: I am sorry that I failed to mention that in our swine remissions and exacerbations of the symptoms seem to be a very common feature until the disease has progressed for 2 to 3 months. After bony changes have begun to occur in the joints the disease usually progresses at a more uniform rate. However, remissions and exacerbations in the early stages of the disease are common features, as well as lameness which seems to have a tendency to shift to various joints. During the first 2 weeks the animals seem to be very lame in all leg joints. A week or two later one will observe that the lameness has shifted so that only one or two joints are involved. At this time, we begin to see marked swelling of the affected joints.

DR. ROBERT STECHER (*Cleveland, Ohio*): Several years ago I visited the Equine Experimental Station in Newmarket, England, and they described an epidemic that they had had a year or so before in foals of acute arthritis which seemed similar to this, and I saw many preserved specimens. While I was there a new case was brought in and I saw the autopsy; the joints looked very much like the joints that you have shown here. They had been unsuccessful in isolating an organism in this disease.

I also saw dried specimens of the spines of horses that showed various signs of spondylitis and ankylosis and spur formation, and so forth, which looked very much like the specimen that you showed here. I have picked up specimens on the prairie in Wyoming, from horses that had been destroyed, that showed these lesions again. This seems to indicate that perhaps the infection is more important than we had heretofore thought.

DR. R. R. WILLIAMS (*Bethesda, Md*): We also had the opportunity of testing some of these sera from swine with rheumatoid disease, and our results were essentially the same as Dr. Ziff's. All our tests were negative, but I would suggest that possibly the sensitization of the sheep cells with swine antiserum to sheep cells might produce some agglutination. We know that bovine gamma-globulin is quite different in reactivity from the agglutinating material in human rheumatoid serum, and that there is little difference between human and rabbit gamma-globulin.

DR. NEHER: I should like to say a word in regard to blood proteins. Several years ago some preliminary work was done by Mrs. Lois Koenig at our laboratory, using electrophoretic procedures to determine the changes in the blood globulins. In this particular work the investigator showed a rather nice correlation between the protein changes in the blood of arthritic swine and those in the blood of the human arthritic patient. In arthritic swine the albumen content fell to about two-thirds of normal, while the levels of beta- and gamma-globulin rose to 50 and 30 per cent. above normal. A 10 per cent. increase in the concentration of fibrinogen was also observed.

These findings may serve to illustrate another of the many parallels between the disease in swine and rheumatoid disease in man.

Chemical Changes in Connective Tissue resulting from Injury. By ANNA-MAE P. A. LUFT, and R. H. PEARCE, *London, Ont., Canada.**

The morphological changes in the tissues affected by the rheumatic diseases resemble in many respects, the inflammatory response that follows local injury to connective tissue. Accordingly, a study of the chemical changes that followed the production of a necrotizing lesion in the skin was undertaken with the hope of elucidating the pathological process associated with the "rheumatic" diseases.

Male Sprague-Dawley rats were injected intracutaneously with 0·5 ml. 1 per cent. croton oil in corn oil. At intervals following the injection, the injected and uninjected control skin was analysed by a method for the separation of normal rat skin into ground substance, interfibrillar cement, and collagen. Parallel histological studies were made.

Fibrinoid degeneration involved a marked fall in the hydroxyproline of the collagen fraction with little change in its glycoprotein content. Simultaneously, the free acid mucopolysaccharide and mucoprotein of the extrafibrillar fractions increased. The initiation of repair was associated with a marked systemic rise in the glycoprotein content of the collagen and a fall in the extrafibrillar carbohydrate and hydroxyproline. The hydroxyproline content of the collagen increased as it matured.

* This investigation was supported by the Canadian Arthritis and Rheumatism Society and the Division of Medical Research of the National Research Council of Canada.

Discussion.—DR. THOMAS G. KANTOR (*New York, N.Y.*): Did the determination of the factor of dry weight take into account the large influx of inflammatory cell material in these lesions? This factor would tend to give abnormally low values of hexosamine and collagen in lesions with large amounts of cells as opposed to those with smaller numbers when related to dry weight.

DR. PEARCE: The dry weights included the solid materials from any cells that entered the tissue. As you can appreciate, the measurement of the material contributed by the cells would be extremely difficult. We hope in future to perform analyses upon a known area of skin so that results may be expressed as changes per unit area rather than in terms of dry weight, as here. Certainly the contribution of the cells may be significant and should be assessed, if possible, in future experiments.

DR. KARL MEYER (*New York, N.Y.*): I want to give a warning against the adoption of this classification, especially so far as mucoid is concerned. We have isolated this substance in the polysaccharide called keratin sulphate which contains both hexosamine and hexose and is a polysaccharide, but would not follow the classification adopted here.

Secondly, in this type of extraction you find terrific interactions of the proteins with polysaccharides and of the polysaccharides with themselves; I would rather see some isolation of definitive compounds, if possible, before drawing this conclusion that there is, especially with the development of reticulin, mucoid and not polysaccharide involvement.

DR. PEARCE: There is no doubt that the materials which we have called, for simplicity's sake, "mucoid" could actually be keratosulphate or some similar compound. If a keratosulphate-like compound were bound covalently to protein, the product would resemble the mucoids of connective tissues. I attempted to give a clear definition of the type of chemical change that would be attributed to "mucoid", "acid mucopolysaccharide", and so on. Such terminology serves primarily as an aid in discussion. Thus the validity of the conclusions we have drawn is limited by the uncertainty regarding the chemical nature of the compounds involved in the biological processes.

Experimental and Clinical Studies of a Heparin-Precipitable Fraction of Fibrinogen. By RICHARD T. SMITH, *Minneapolis, Minn.*

A catastrophe of widespread haemorrhage and necrosis, the generalized Shwartzman reaction, occurs regularly after either two appropriately spaced intravenous injections of Gram-negative bacterial endotoxin or a single injection of endotoxin in combination with certain high molecular weight acidic polymers, such as dextran sulphate. An explanation for these lesions has been found in extensive occlusion of small vessels by hyaline material with staining characteristics of fibrinoid. This fibrinoid material has further been shown to consist in part of fibrinogen, probably derived from the circulating blood. Attempts were therefore made to identify an alteration of circulating fibrinogen occurring after injection of endotoxin which might have staining characteristics and other properties of fibrinoid. As a result of such studies a qualitative change in circulating fibrinogen of rabbits manifested by cold-precipitation in the presence of heparin, was found to occur as a regular response to a single intravenous injection of endotoxin.

Histopathologically, vascular fibrinoid lesions of the generalized Shwartzman reaction in animals resemble strikingly those found in certain human diseases, such as lupus erythematosus, polyarteritis nodosa, acute fulminant rheumatic fever, and fulminant rheumatoid arthritis. It was of interest therefore to examine the the plasma of patients with these diseases for the presence of a similar fraction. In the plasma of severely ill patients with all of the diseases mentioned, and also in those with severe bacterial meningitis, endocarditis, and disseminated malignancy, a cold-insoluble, heparin-precipitable fraction was found in large amounts.

Extension of these studies utilizing a semiquantitative technique has shown that small amounts of the fraction are present in normal human plasma, the mean value being 0·13 g. per cent. Levels in severely ill patients ranged from 0·3 to 0·8 g. per cent. A few children with acute rheumatic fever had levels as high as 1·4 g. per cent. Serial studies of this fraction during the entire course of rheumatic fever, rheumatoid arthritis, acute bacterial infections, and other diseases have indicated that initially high levels return rapidly to normal upon spontaneous inactivation of the disease or as a result of steroid or antibiotic therapy. Whereas in normal persons the ratio between heparin-precipitable fraction and clottable fibrinogen was in the range of 0·3-0·6, in these acutely ill patients, this ratio was most often greater than unity. Correlations were made between the levels of this fraction and fibrinogen, sedimentation rate, C-reactive protein, mucoprotein, and electrophoretically measured plasma protein fractions.

Chemical studies of the fraction indicate that it is closely related to fibrinogen, in its absence from serum, partial clottability, and electrophoretic mobility, but differs from normal fibrinogen in its insolubility at 4° C. in combination with heparin and other similarly charged polymers. Solubility at this temperature is influenced markedly by *p*H, ionic strength, and the presence of calcium or magnesium ions. Detailed studies of solubility, electrophoretic mobility, sedimentation characteristics, and end-group patterns are in progress in an attempt to determine the exact relation of this fraction to fibrinogen.

The data available are consistent with the conclusion that the heparin-precipitable fraction represents a qualitative change of fibrinogen which increases as a reflection of the presence of inflammatory disease. The possible relation of this fraction to fibrinoid deposits in human disease is as yet unknown, but currently under study.

Discussion.—DR. JOSEPH E. WARREN (*Pittsburgh, Pa*): This paper calls to mind the report by Abrams in Great Britain of the apparent resistance of rheumatic patients to the anticoagulant action of heparin *in vivo*. Perhaps the fibrinogen fraction which precipitates with heparin may also be the factor which interferes with the anticoagulant action in rheumatic patients.

DR. SMITH: I am aware of Abrams' work and find it of great interest. I have tried to perfect their technique

in my laboratory, but without success as yet. Therefore, I have no comment to make except that their findings may have some relationship to this.

Isolation of Hyaluronic Acid from Synovial Fluid by Electroconvection. By SAUL ROSEMAN, DONALD R. WATSON, IVAN F. DUFF, and WILLIAM D. ROBINSON, *Ann Arbor, Mich.*

Electroconvection has been used in attempts to isolate undegraded hyaluronic acid (HA) or its protein complex from bovine and pooled human synovial fluid (SF). With the *p*H 7 and temperature below 1° C., a portion of the HA acted in the expected manner and was transferred from the upper to the lower reservoir. An appreciable fraction of the HA was deposited on the channel closest to the anode in the form of a gel (G_1). From 60 to 70 per cent. of the total HA could be recovered as G_1 when the SF was introduced in a continuous manner into the bottom reservoir and forced against the convection currents into the channel. The remaining HA was found in the lower reservoir at the end of the experiment. A portion of the soluble HA could be deposited by subjecting the reservoir solution to electroconvection. When G_1 was dissolved in buffer and treated again in the same manner, it yielded a gel (G_2). Repeating the procedure once more yielded G_3. Analysis showed that the ratio of mg. protein/mg. HA in these materials was as follows: dialysed SF 33·5; G_1 1·8; G_2 0·25; G_3 0·13. The purification factor of HA with respect to protein is therefore about 258 in G_3 compared with SF. Preliminary viscosity studies indicate that the gels and SF exhibit approximately the same relative viscosities at equal concentrations of HA.

It was of interest to find that heparin and sodium chondroitin sulphate did not deposit as gels under the conditions described above. After chondroitin sulphate was added to synovial fluid, the HA was isolated (G_2) with no detectable chondroitin sulphate contamination.

Discussion.—DR. MORRIS ZIFF (*New York, N.Y.*): The viscosity of the hyaluronic preparations seems to be independent of how much protein is present in the preparation. Do you feel then that protein binding has no influence on the viscosity of the hyaluronic acid in the synovial fluid?

DR. ROSEMAN: It has been known for a long time and other workers have established that the viscosity of joint fluid, despite its high protein concentration, is almost completely dependent upon the polysaccharides. I also remember that Drs. Ropes and Bauer's group was involved in this some time ago. The addition of trypsin to the fluid does not result in an appreciable decrease in viscosity. The addition of hyaluronidase results in an immediate and very sharp decline of viscosity to the viscosity of serum, so that it would appear as though the protein is not too significant.

DR. MORRIS ZIFF: What about the protein binding? Do you think there is actual binding or not?

DR. ROSEMAN: This is quite another matter. I cannot say that we agree with Ogston, or Blix, or Meyer. We have gone down to a preparation which is roughly 10 per cent. protein, and exhibits the same viscosity as our other preparations of much higher protein content. If one wanted to take the data of Ogston at face value, one would have to conclude that these results do not support his contention. But we should wait a little longer and see whether we can get a preparation free of protein by our best analytical techniques; if it retains the same viscosity we should have to conclude that the viscosity of joint fluid is dependent upon the polysaccharide alone.

DR. R. H. PEARCE (*London, Ont., Canada*): Do you feel that your technique might have selected from the synovial fluid the hyaluronate that was undegraded and uncombined with protein? If this were the case, your finding that the isolated hyaluronate was undegraded and protein-free would signify only that a part of the hyaluronate of synovial fluid was in this state.

DR. ROSEMAN: We do not recover 100 per cent. of the polysaccharide that goes in. The soluble fraction is always down in the lower reservoir. If you re-run the soluble component you recover an appreciable yield of gel, the same type of yield as is obtained with the whole fluid, *i.e.* 60 per cent. We have not yet repeatedly electroconvected the lower reservoir material.

Assuming there may be several types of hyaluronate, it is interesting to note that in just a single experiment chondroitin sulphate of molecular weight of 17,000 yielded no gel. When an aqueous extract of fresh cartilage was made, following the technique of Schubert and co-workers, we did obtain a gel which was rich in chondroitin sulphate; so I think we are selecting the protein polysaccharide components, not the polysaccharide alone.

The important concept concerning this protein complex is whether it is ionic or non-ionic. Dr. Meyer showed a long time ago that you could precipitate the polysaccharide with protein at the right *p*H, and you can obviously get a complex of the ionic or salt type. He also pointed out that this might exist in synovial fluid, but this is not at all the type of complex dealt with by Ogston's group.

DR. WARD PIGMAN (*Birmingham, Ala*): As Dr. Roseman knows, this problem is not quite as simple as it might appear on the surface. For example, we have just the elementary problem of measuring viscosity with such materials and such systems. Frequently these materials are not truly viscous, and do not obey the laws for truly viscous solutions, so that one's results depend upon the particular apparatus and method used. The question is particularly complicated in dealing with the concentrations in synovial fluid, because the ideal viscosity will be demonstrated only in very dilute solutions.

This does not reflect on Dr. Roseman's work, but we have to keep our minds open. We have not decided yet whether a complex is formed between protein and hyaluronic acid or other materials in the actual synovial fluid.

DR. ROSEMAN: This does reflect—I think rightly—on the data reported. When the materials are not Newtonian, they do not behave in an ideal manner. We are only talking about relative viscosities and we have run all the samples through the same viscosimeter under the same conditions so that we can plot them on the same curve. I make no claims concerning the absolute or intrinsic viscosity.

DR. WARD PIGMAN: I think it might be as well to drop

the term "viscosity" in these kinds of measurements. We are now involved in measuring or attempting to measure something which you might call "viscosity", but we are planning to call it "flow rate", or something like that.

DR. ROSEMAN: You are now, aren't you, rewriting your book, and as soon as you come out with a new term I shall be very happy to adopt it.

DR. KARL MEYER (*New York, N.Y.*): In this discussion it is not a matter of whether there are, under certain circumstances, complexes with protein. The question is whether the physical properties of normal synovial fluid or of any synovial fluid are determined by hyaluronic acid or by a complex of definitive nature, as Ogston has said.

I think the experiments which Dr. Roseman described answer this in the negative, because Ogston has said, using the same or similar criteria to those of Dr. Roseman, that the most sensitive physical property was the viscosity. This is a perfectly justifiable term to use; whether it is known as a butonium or non-butonium type of viscosity, it is still viscosity.

Dr. Ogston, who is an extremely capable physical chemist, has come to the conclusion that the physical properties of synovial fluid are determined by a protein complex containing at least 25 per cent. protein. Now, by a rough calculation from Dr. Roseman's figures, the protein concentration is in the order of 10 per cent. Is that right?

DR. ROSEMAN: Yes.

DR. KARL MEYER: This in itself would abolish the argument which Ogston used. Furthermore, Dr. Blumberg in our laboratory has measured viscosity, not the relative but the absolute viscosity, one of the reduced viscosities, and by all our criteria the hyaluronic acid (which we isolated not from synovial fluid, but from streptococcus and from a human tumour) had exactly the same properties, not only in viscosity but in all physical characteristics, as Ogston ascribed to the protein complex.

The protein content of our material was less than 0·3 per cent. protein.

These experiments clearly show that the physical properties of hyaluronic acid solutions are determined by the hyaluronic acid itself and not by any complex whatsoever of hyaluronic acid with protein.

DR. MARIAN W. ROPES (*Boston, Mass.*): I think it is important to describe the type of viscosity being measured because I feel, with Dr. Pigman, that we cannot use the general term "viscosity". Ogston found the biggest change in viscosity measurements as a change in anomalous viscosity, the variation of viscosity with different flow rates.

Experiments done in the presence of buffer do not necessarily prove whether or not there is a combination of protein and polysaccharide in the original or native state. As soon as the fluid or material is put in any buffer of any type, that it is no longer in its native state has been one of the difficulties in solving the problem which has been presented under so many different facets over the years.

DR. ROSEMAN: It seems to me that we have left the native state as soon as we take the sample out of the joint.

DR. MARIAN W. ROPES: That is true.

DR. ROSEMAN: There is always that limitation. We always have to work within the limitations imposed by our methods. So far as we know, this is the most sensitive (or the least vigorous) method for isolation.

Concerning the viscosity question, all we can do and all we are interested in doing at the moment is to determine that the preparations, under the same conditions as the initial fluid, exhibit the same viscosity, using the same viscosimeter.

Concerning the problem of the buffer, I feel that the viscosity of the joint fluid as it is withdrawn from the animal does not change markedly when it is dialysed against the buffer.

DR. WARD PIGMAN: In the first place, as Dr. Ropes has shown, salts have a tremendous influence on the viscosities of these types of compounds. I do not know how you take this factor into account.

The other thing is that very few people are dealing with normal fluid; most investigators have worked with arthritic joint fluid or cattle fluid, which are of a very much lower viscosity than normal fluid. The normal picture is quite different from that for arthritics. What we want to know in talking about a combination of protein and hyaluronic acid is how it appears in the normal fluid, and only secondarily what happens in the synovial fluid in the arthritic joint.

DR. ROSEMAN: I hope Dr. Pigman can send us some normal fluids to run through, for we are having difficulty getting enough.

Chromatographic Separation of S^{35}—labelled Materials from Cartilage and Bone of Suckling Rats following Administration of Sodium Sulphate-S^{35}. By D. DZIEWIATKOWSKI, N. DIFERRANTE, and F. BRONNER,* *New York, N.Y.*

Chondroitin sulphate is known to be present in cartilage and its presence in bone has been suspected. The suggestion has been made that this polysaccharide plays a role in endochondral ossification. Recently the feasibility of using S^{35}-labelled sulphate for the study of the metabolism of chondroitin sulphate was demonstrated and the possible presence of other sulphated materials was suggested. A chromatographic separation of sulphated components in cartilage and bone was therefore undertaken.

Following the administration of 100 μc. S^{35}-sulphate intraperitoneally to each of ten rats on their 7th day of life, the animals were sacrificed in pairs at certain intervals. After dissection the epiphyses of the tibiae and femora were separated from the diaphyses, which were then freed of bone marrow. Alkaline extracts were prepared and, following adjustment of *p*H with acetic acid to 6·5-6·7, a portion of each extract was chromatographed on a column of Dowex-2. Solutions of increasing chloride concentration were used to elute the S^{35}-containing materials. Extracts of the epiphyses contained about 90 per cent. of the total sulphur-35 in the tissues; an average of 75 per cent. of the activity was extracted in the case of the diaphyses. Recovery from the columns in all cases was nearly 100 per cent.

Six peaks of radioactivity were demonstrated in the chromatograms. The sulphate-35 in one peak was

* Fellow of Helen Hay Whitney Foundation, 1954-55; Fellow of the Arthritis and Rheumatism Foundation.

associated with inorganic sulphate, in another with material which behaved like chondroitin sulphate. Glucuronic acid and hexosamine were detected in the remaining four peaks.

The sulphur-35 activity associated with the inorganic sulphate peak diminished rapidly with time after administration of the S^{35}-sulphate. The concentration of sulphur-35 in each of the other peaks increased rapidly up to about the 24th hour; thereafter it decreased slowly, but at a rate that was different peak to peak.

Degenerative Joint Disease in Obese and Non-Obese Mice of Strain Y′. By MARTIN SILBERBERG and RUTH SILBERBERG, *St. Louis, Mo.*

In previous experiments carried out in mice of various strains, articular ageing and the evolution of degenerative joint disease were found to be influenced by nutritional factors: A high-calorie high-fat diet accelerated articular ageing and increased the incidence of degenerative joint disease, while underfeeding delayed these changes. Under the influence of a high-fat diet overweight occurred in mice of some strains. However, there was no definite correlation between weight increase and the incidence of degenerative joint disease, and additional investigations along these lines seemed indicated. Mice of strain YBR/Wi present suitable test material to analyse further the effect of obesity on degenerative joint disease. This strain comprises two types of individuals which differ, as far as is known, in regard to only one gene. One type possesses a gene Y′, the other type does not possess this gene. Bearers of the Y′ gene are characterized by yellow coat colour and by a tendency to develop obesity, when fed enriched diets. Animals not possessing this gene are grey-coated and do not become obese, when kept on such dietary regimens. Grey-coated and yellow-coated mice of both sexes were fed through life (*a*) a stock diet, (*b*) a high-fat diet, or (*c*) a high-carbohydrate diet respectively.

Diets enriched in animal fat may accelerate the onset and increase the incidence of degenerative joint disease irrespective of obesity. Excessive obesity is a contributory factor in the pathogenesis of osteo-arthritis. Findings in the pancreas, the uterus, and the bony diaphyses suggest that endocrine disturbances exist in YBR mice and that these metabolic disturbances may, in turn, play an aetiological role in the pathogenesis of degenerative joint disease in these mice.

Discussion.—DR. F. BRONNER (*New York, N.Y.*): Did you have an opportunity to study the sections which would reveal possible parathyroid enlargement in these mice?

DR. SILBERBERG: We found no changes in the parathyroids in these mice.

DR. IRVIN STEIN (*Philadelphia, Pa*): In your sections, what was the problem in regard to the capillaries? I was interested in whether you found sections of capillary hypertrophy.

DR. SILBERBERG: The criteria were the same as those postulated for humans. Therefore, we think we are safe in considering the disease in the mouse as an analogue of human degenerative joint disease.

DR. EVAN CALKINS (*Boston, Mass.*): Did I understand correctly that 60 per cent. of the yellow mice had developed amyloidosis?

DR. SILBERBERG: Yes, in both grey and yellow mice.

DR. EVAN CALKINS: Did this high percentage of grey and yellow mice develop amyloidosis?

DR. SILBERBERG: Yes, irrespective of sex and irrespective of diet.

DR. EVAN CALKINS: Have other strains of mice that you may have observed shown this incidence of amyloidosis?

DR. SILBERBERG: No, in our other strains of mice we have rarely seen amyloidosis. In the Y′ mice, there was a considerable amount of amyloid deposited. In mice of some other strains spontaneous amyloidosis occurs; for instance in Strain A it is associated with pyelonephritis, and also reaches a very high incidence.

DR. EVAN CALKINS: I was interested because we have tried to produce amyloidosis in mice by various measures, and in various strains, and we have found a very low incidence.

DR. SILBERBERG: I think, in the National Institute of Cancer at Bethesda, 10 or 12 years ago, this very high incidence of spontaneous amyloidosis was observed in mice of Strain A.

Studies on the Diurnal Pattern of Urinary 17-Hydroxycorticoid and 17-Ketosteroid Excretion in Patients with Rheumatoid Arthritis. By S. RICHARDSON HILL, JR., HOWARD L. HOLLEY, WILLARD R. STARNES, and LESTER L. HIBBETT, *Birmingham, Ala.*

Experimental evidence would indicate that adrenal cortical function is normal in the majority of patients with rheumatoid arthritis, although there are theoretical objections to the contrary. Because of the availability of more precise techniques for measuring adrenal cortical secretory activity and because of the accumulating evidence for a fairly consistent pattern of steroid excretion in normal subjects, this study of adrenal cortical function in patients with rheumatoid arthritis was undertaken.

Four groups of subjects were studied:

(1) Nineteen ambulatory normal male dental students;
(2) Five hospitalized young male patients with little physiological effect from various diseases;
(3) Six hospitalized male patients with active rheumatoid arthritis;
(4) Five hospitalized male patients of comparable age with non-rheumatic chronic diseases.

Urine specimens were collected from 7 a.m. to 1 p.m., and 1 p.m. to 7 p.m., and one specimen from 7 p.m. to 7 a.m. for one or more days on all subjects for determination of the total 17-hydroxycorticosteroid and 17-ketosteroid content.

There is no appreciable effect of hospitalization alone on the total 24-hr urinary output of 17-hydroxycorticosteroids or of 17-ketosteroids. The characteristic morning increase in steroid output observed in normal subjects is much less striking in hospitalized patients, resulting in a flattened diurnal excretory pattern. Hospitalized patients with rheumatoid arthritis and patients

with non-rheumatic chronic diseases have a similarly flattened diurnal steroid excretory pattern. The total 24-hr urinary output of 17-hydroxycorticosteroids is lower in patients with rheumatoid arthritis and with non-rheumatic chronic diseases than in the other two groups of subjects studied.

The ratio of 17-hydroxycorticoids to 17-ketosteroids is lower in the patients with rheumatoid arthritis than in the other groups.

Discussion.—DR. JOSEPH E. WARREN (*Pittsburgh, Pa*): We have also been conducting diurnal corticoid studies, but prefer to depend on plasma corticoid assays. On a chart summarizing our pertinent data the vertical scale represents concentration of hydrocortisone in plasma, and the horizontal scale shows the 24 hours starting at 8 p.m. Observations were made every 3½ hours. The average levels were plotted for nine patients with rheumatoid arthritis and nine comparable controls. The patients were ambulatory, showing minimal to moderate activity of the rheumatic process; none had been on cortisone, and aspirin was omitted during the study. Peak levels occur in the middle of the chart and represent the assays at 7 a.m. before rising from bed and very shortly after awakening. The chart shows a definite diurnal variation in the plasma levels in both groups, the peak levels being similar in time and degree, and there is also a tendency for the levels at 3.30 a.m. to be higher in the rheumatoid patients than in the controls. This might well account for some of the flattening of the urinary excretion levels since it reduces the slope of the subsequent rise to the morning peak. The cause of this early morning difference in plasma levels will require further study.

DR. HILDEGARD WILSON (*Bethesda, Md*): In our laboratory at New York University we have also been analysing urinary steroids in two male subjects with rheumatoid arthritis. For comparison we used a pool of urine from healthy young men, worked up by identical procedures.

We made detailed analyses using paper chromatographic separation into twelve fractions, then applying a battery of corticosteroid assays to each eluate, and finally carrying out further procedures for purification and characterization of steroids.

In agreement with Dr. Hill's findings on hospitalized patients, one of our rheumatoid subjects was well below the controls in his content of polar corticosteroids, as measured by the formaldehydogenic and chromic-acid-ketosteroid assays. These polar compounds would account for most of the titre obtained by the Porter-Silber reaction which Dr. Hill used.

Our assays also determine the less polar corticosteroids, and the titres of these substances, in contrast, were elevated to about twice the normal in both the rheumatoid subjects. As a consequence, both titres of total corticosteroids were above those of the normal controls.

In a search for the metabolites responsible for these differences, identification procedures showed two polar metabolites, Compound E and Compound tetrahydro E, to be present in the normal urine but absent in the one rheumatoid so studied. Moreover, five less polar metabolites were present in the patient's urine, but absent, or found only in traces, in the controls.

When ACTH was given to the rheumatoid subject, Compounds E, F, tetrahydro E, and tetrahydro F were identified in his urine. Some of the "abnormal" less polar compounds diminished or disappeared, while others remained.

These observations suggest that the "steroid abnormality" in this subject was related to the effectiveness of his endogenous ACTH rather than to any inability of his adrenal cortex to make the normal complement of hormones. Without extra ACTH the biosynthetic reactions in his adrenal cortex seem to have produced less of the fully hydroxylated hormones, and more intermediates of lower oxygenation. Administration of exogenous ACTH changed these processes towards normal. Further studies are required to see whether or not this picture is characteristic of rheumatoid arthritis.

DR. HILL: In terms of theoretical knowledge to be gained, I think that Dr. Wilson's studies represent the most fruitful approach to the subject of any that are now being employed. The absolute determination of the qualitative pattern of adrenal cortical secretion might once and for all give us the answer, *in humans*, to the question that has been raised by Dr. Hans Selye regarding the abnormal ratios of phlogistic to anti-phlogistic hormones in certain "rheumatic disease states" in animals. Dr. Wilson's experience on one patient should certainly be extended.

DR. ROBERT S. HOWELL (*Miami, Fa*): The diurnal variation may also reflect the glomerulo-filtration rate, which is known to affect the rate of excretion of hydroxycorticosteroid.

DR. HILL: Thorn and Laidlaw (1954) have shown that the characteristic diurnal pattern of adrenal cortical secretion persists in normal subjects despite forced inactivity in bed for 24 hours, a reversal of the normal working schedule, 24-hour starvation and alteration in fluid intake sufficient to induce an overnight polyuria. In considering the mechanism by which the diurnal variation of corticosteroid output is controlled, it is of interest to note that the urinary excretion of 17-hydroxycorticoids in patients with Addison's disease receiving maintenance doses of cortisone or hydrocortisone by continuous intravenous infusion at a constant rate, contrasts sharply with that seen in normal individuals. This suggests that this cyclical rhythm does not reflect variation in the intermediary metabolism *or excretion* of adrenal cortical steroids, but rather reflects diurnal swings in pituitary-adrenal or hypothalamic-pituitary-adrenal secretory function.

DR. EVAN CALKINS (*Boston, Mass.*): While we are on the subject of diurnal variations, I should like to point out that Dr. Daniel Bachman, in our laboratory, in some preliminary studies, has shown that the normal diurnal variation in urinary chloride excretion appears to be absent, or reversed, in patients with active rheumatoid arthritis.

DR. VINCENT C. KELLEY (*Salt Lake City, Utah*): In agreement with Dr. Wilson's comments, I feel that one should take care not to draw too sweeping conclusions regarding the normality of adrenal function on the basis of 17-ketosteroid and 17-hydroxycorticosteroid excretion. We are finding in many conditions now that alterations in the pathways of steroidogenesis, resulting in different end-products and different concentrations of various intermediates of steroidogenesis, may be of more significance than the total amount of 17-hydroxycorticosteroid or 17-ketosteroid groups excreted.

We must remember that there are many different methods for measuring 17-ketosteroids and several for 17-hydroxycorticosteroids, and that with different methods the results are different. In view of the somewhat elevated 17-ketosteroid excretions, it is worth recalling that several workers have indicated that the excretion of 17-ketosteroids is decreased in rheumatoid arthritis.

In our studies in children with juvenile rheumatoid arthritis, the plasma levels of 17-hydroxycorticosteroids, done by the technique of Nelson and Samuels (1952), have been low, whereas the urinary excretion of these steroids has been within normal limits. The excretion of "17-ketogenic steroids" has been shown to be low in rheumatoid arthritis; initially this was reported as being about 40 per cent. lower than normal, but this figure has now been revised. Appleby and Norymberski (1955) studied the 21-deoxyketols and concluded that these were normal in patients with rheumatoid arthritis; but in the only very acute case of rheumatoid arthritis in their series the 21-deoxyketols were approximately twice as high as in any other patient in the entire series.

It would appear that there is considerable evidence suggestive of abnormal adrenal function in patients with rheumatoid arthritis, but no one is in a position to define the exact status of pituitary adrenal function in such patients, so that many studies such as Dr. Hill's are needed to clarify this problem.

DR. HILL: The total 17-hydroxycorticosteroids were determined by a modification of the method of Reddy, Jenkins, and Thorn (Reddy, 1954). This is a butanol extraction method with a Porter-Silber colour reaction (Porter and Silber, 1950). The 17-ketosteroids were extracted by a modification of the method of Drekter and others (1952), and the colorimetry was performed as in the procedure of Holtorff and Koch (1940).

Using these methods in our laboratory, we have been able to obtain very consistent and reproducible results.

As to the question of normal adrenal cortical function in patients with rheumatoid arthritis, I am of course speaking in terms of the techniques employed in these studies—that is by measuring total 17-hydroxycorticosteroids and 17-ketosteroids. I should not like to leave the impression that I think adrenal cortical function is either normal or abnormal in patients with rheumatoid arthritis. This subject is still open to investigation.

Many studies show a low degree of urinary 17-ketosteroids in patients with rheumatoid arthritis; there are, however, almost as many reports showing normal or increased levels of 17-ketosteroids.

DR. WILLIAM D. ROBINSON (*Ann Arbor, Mich.*): I should like to add my congratulations on this excellent work, and to add a word of warning with respect to its interpretation that is in no way intended as a criticism. We must be careful in interpreting the pattern of steroid excretion in the urine as necessarily representing what the adrenal is releasing into the blood. Information on what happens to these steroids between the time they leave the adrenal and the time they are determined in the urine is extremely important. Conn and others (1954) have developed a test in which the pattern of excretion of 17-ketosteroids and 17-hydroxycorticosteroids is determined after test doses of hydrocortisone, or, preferably, Compound S. Dr. Duff and others from our laboratory have applied this test to patients with rheumatic diseases and found clear-cut differences in the proportions of such steroids which are excreted as 17-ketosteroids and as 11- or 17-hydroxycorticosteroids. We must be careful in this very complicated problem to distinguish between what may be produced by the adrenal in terms of abnormal steroid production and what may actually constitute an abnormal metabolism of the steroids before they appear in the urine.

DR. HILL: I agree that we cannot say that the changes found in steroid levels represent changes in adrenal cortical function. It is entirely possible that the differences noted represent alteration in steroid metabolism rather than in adrenal cortical secretory activity. Indeed, such alterations in steroid metabolism have been shown to occur by the use of radio-actively tagged hydrocortisone.

REFERENCES

Appleby, J. I., and Norymberski, J. K. (1955). *Annals of the Rheumatic Diseases*, 14, 172.
Conn, J. W., Fajans, S. S., Louis, L. H., and Seltzer, H. S. (1954). *J. Med.*, 43, 79.
Drekter, I. J., Heisler, A., Scism, G. R., Stern, S., Pearson, S., and McGavack, T. H. (1952). *J. clin. Endocrinol.*, 12, 55.
Holtorff, A. F., and Koch, F. C. (1940). *J. biol. Chem.*, 135, 377.
Porter, C. C., and Silber, R. H. (1950). *Ibid.*, 185, 201.
Reddy, W. J. (1954). *Metabolism*, 3, 489.
Thorn, G. W., and Laidlaw, J. C. (1954). *Trans. Amer. clin. climatol. Ass.*, 65, 179.

Influence of Salicylates on the Pituitary-Adrenal System in Normal and Rheumatic Human Subjects. By ALAN K. DONE and VINCENT C. KELLEY, *Salt Lake City, Utah.*

Considerable indirect evidence has suggested that salicylates produce pituitary-adrenal stimulation and that this effect accounts, at least in part, for their anti-rheumatic properties. The present report deals with more direct observations on the effects of salicylate on the pituitary adrenal system, obtained by measurements of adrenal hormones in blood and urine. Plasma 17-hydroxycorticosteroid (17-OHCS) concentrations were determined by the method of Nelson and Samuels (1952) and Eik-Nes, Nelson, and Samuels (1953); urinary 17-OHCS by the method of Glenn and Nelson (1953).

Non-rheumatic individuals with salicylate *intoxication* were found uniformly to have markedly elevated plasma 17-OHCS concentrations.

Normal human subjects given salicylates in usual therapeutic doses failed to show consistent elevations in circulating levels of 17-OHCS. However, salicylate administration was accompanied by greater fluctuations in the plasma concentrations of these steroids than were found as normal diurnal variations. Both increases and decreases in steroid concentrations were significantly greater on days of salicylate administration than on control days. The urinary excretion of 17-ketosteroids was unchanged, while significant reduction in the urinary output of 17-OHCS was observed. These data are interpreted as suggesting a dual effect of salicylates on the pituitary-adrenal system:

(1) increased production of adrenal steroids due to pituitary stimulation;
(2) an increased rate of removal of these steroids from circulation by a means other than urinary excretion—(?utilization).

Additional evidence of this dual effect has been obtained by studies on the influence of salicylate on the half-life of exogenous hydrocortisone. Salicylate administration

decreases the half-life (increases the rate of disappearance) of exogenous hydrocortisone and also produces an increased release of steroids by the adrenal cortex.

Rheumatic fever patients treated with salicylates uniformly showed no increase in circulating or urinary 17-OHCS levels. Indeed, in contrast to non-rheumatic individuals, even those rheumatics who developed severe salicylate intoxication failed to develop raised plasma 17-OHCS concentrations. Prolonged salicylate treatment for rheumatic fever resulted in a post-therapy diminution in 17-OHCS response to ACTH of a degree similar to that produced by prolonged cortisone therapy.

Discussion.—DR. S. RICHARDSON HILL, JR. (*Birmingham, Ala*): What is the relationship between the free and the total, including both free and conjugated, urinary 17-hydroxycorticosteroid levels? The decreased urinary *free* 17-hydroxycorticosteroid levels reported following salicylates could be due to an increased conjugation of these steroids, and might not necessarily represent an increased rate of removal of these steroids from the circulation by a means other than urinary excretion.

DR. DONE: Unfortunately I cannot give you any data at the present time. By "free", do you mean unconjugated?

DR. S. RICHARDSON HILL: Yes.

DR. DONE: We have had considerable difficulty in establishing a technique for determining conjugated corticosteroids, but we now have it worked out and expect to have some data shortly.

DR. JOHN N. SWANSON (*Toronto, Ont., Canada*): At what time after the intravenous dose were these plasma levels measured? Some 4 years ago, working in Dr. Walter Bauer's group, I observed that the eosinophil count fell by more than 50 per cent. at the end of 5 hours after a large dose (4 g. or more) of sodium salicylate or aspirin had been administered orally. Doses of less than 4 gr. had no detectable effect, even though eosinophil counts were carried out hourly for 8 hours. If this fall is accepted as being secondary to adreno-corticoid liberation, it seems that it only occurs when large, nearly toxic, doses of salicylates are given, and may not therefore be due to the pharmacological action of the drug.

DR. DONE: These levels were taken immediately before the next dose of salicylate was to be given. In most of these patients salicylate was given every 6 hours, so the sampling interval would be approximately 5½ to 6 hours after the administration of the previous dose.

DR. HOWARD F. POLLEY (*Rochester, Minn.*): What was the plasma salicylate level in the patients with salicylate intoxication, and for how long had the symptoms of toxicity been present? Were the patients receiving any treatment for the salicylate toxicity?

DR. DONE: So far as duration of salicylate intoxication is concerned, we did not include patients in this group if they showed no more than the usual signs of intoxication one looks for in treatment of a rheumatic. In those included, the duration of administration leading to intoxication ranged from 2 hours to 4 days, and in each instance the symptoms were very severe. The salicylate levels ranged from 46 to 88 mg. per cent. The salicylate levels and symptomatology were comparable to those in the non-rheumatic individuals.

At the time when the samples were taken, the salicylate intoxication was not being treated.

DR. HILDEGARD WILSON (*Bethesda, Md*): If salicylates exert their beneficial effects in rheumatic diseases because they increase adrenocortical activity, it seems to me that one would expect to see an increase in blood and urine steroids with a dosage of salicylates sufficient to produce a therapeutic result. I wonder whether you could give any idea of how the level of plasma 17-hydroxycorticoids on your dosage of salicylates compares with that resulting from the minimum amount of ACTH which produces the same beneficial effect. This might indicate whether or not the therapeutic results were both due to the same degree of adrenocortical stimulation.

DR. DONE: I can speak only of the levels in intoxicated individuals since they are the only ones in whom we have seen them consistently elevated. The high steroid level observed in previously normal people with intoxication was approximately the same as we see after the intramuscular administration of 25 mg. of ACTH—that is, the response was essentially comparable. I have no data on the minimal dose of ACTH as compared with the minimal dose of salicylates which will produce this effect.

REFERENCES

Eik-Nes, K., Nelson, D. H., and Samuels, L. T. (1953). *J. clin. Endocrinol.*, **13**, 1280.
Glenn, E. M., and Nelson, D. H. (1953). *Ibid.*, **13**, 911.
Nelson, D. H., and Samuels, L. T. (1952). *Ibid.*, **12**, 519.

Hip-Socket Arthroplasty. A Method of Surgical Treatment of Degenerative Arthritis of the Hip Joint. By MARSHALL R. URIST, *Los Angeles, Calif.*

This is a presentation of a procedure of arthroplasty developed from a study of the biomechanics of the hip joint, histophysiological observations of joint repair, and clinical experience with a hip-socket attached to the pelvis.

Special surgical instruments have been designed for implanting the socket through a postero-lateral approach. The hip-socket is a self-sustained lining for the acetabulum, made of vitallium, and is stable enough to allow motion immediately after the operation. The socket is open in the centre to contain fibrocartilage and mucin-forming tissues as a source of lubrication inside the joint. It encloses only half of the head of the femur and thereby permits a wide range of motion.

The morphological and chemical structure of a pseudarthrosis and a functioning arthroplasty are so similar that it is reasonable to assume that basically the two conditions involve the same connective tissue cell process. Proliferation of fibrous connective tissue and fibrocartilage produce the earliest form of repair. Friction and motion between surfaces around the rim of the joint and in the acetabular fossa precipitates ground substance and produces fibrinoid, mucin, and mucinous fluid. During the first year, the surface of the head consists of dense fibrous tissue and fibrocartilage coated with *fibrinoid*. Further motion and pressure of weight-bearing is necessary for 18 months to 2 or 3 years to produce differentiation of new hyalin-like cartilage from the underlying fibrocartilage.

The joint surface formed from an arthroplasty after years of function resembles articular cartilage. It is not true articular cartilage but it can function as joint cartilage. It becomes increasingly like articular cartilage after a period of years of weight-bearing and after remodelling of the underlying spongiosa to produce an articular cortex of compact bone.

The immediate results obtained in 26 arthroplasties (including six bilateral), were sufficiently good to recommend the method for further trials. The long-term results in individual patients and various types of hip disease are, as yet, not known beyond 1 to two years in five cases, and one year or less in 21 cases. In circumstances favourable for arthroplasty, such as patients with malum coxae senilis, the results were immediate relief of pain, an increase of range of motion, and a stable joint. Hip-socket arthroplasty usually produced a greater range of rotation than cup arthroplasty. More flexion was also obtained; the theoretical explanation for this may be that there was a more normal de-rotation or unscrewing of the head of the femur during the swing phase of the joint motion.

Discussion.—DR. IRVIN STEIN (*Philadelphia, Pa*): I am particularly interested in Dr. Urist's work as an orthopaedic surgeon because he, to me, represents more than just a mechanic, since he has a scientific appreciation of underlying problems.

There are many unpredictables in arthroplasty that bother many men who do a great many of them, and I think he has taken care of one of them very well. This type of prosthesis, which is very different from those that are used commonly now, is more of an acetabular than a femoral head prosthesis, and for certain cases it appears to be really valuable.

Renal Involvement in Progressive Systemic Sclerosis (Diffuse Scleroderma). By GERALD P. RODNAN, GEORGE E. SCHREINER, and ROGER L. BLACK, *Pittsburgh, Pa, Washington, D.C., and Bethesda, Md.*

Progressive systemic sclerosis (diffuse scleroderma) is now recognized as a disorder capable of affecting many organ systems. While the clinical characteristics of cutaneous, gastro-intestinal, and cardio-pulmonary involvement have been well described, the incidence and and severity of renal disease have become more fully appreciated only recently. We have had the occasion to observe the development of abrupt fatal renal insufficiency in seven patients with progressive systemic sclerosis, and present the clinical and pathological features of these cases, together with the findings in one patient who developed only mild renal dysfunction, and one in whom the discovery of extensive renal lesions was not suspected from the clinical course.

When these cases are considered with others previously reported, it appears that renal involvement is of frequent occurrence and ominous significance in the natural history of progressive systemic sclerosis. The initial renal lesion is that of intimal sclerosis and hyperplasia involving primarily the interlobular arteries. When severe, these vessel changes lead to widespread focal cortical infarction and fibrinoid necrosis of the walls of afferent arterioles and glomerular loops. These present the clinical picture of fulminating cardiovascular-renal disease, characterized by severe hypertension, retinopathy, cardiac failure, convulsions, and rapidly progressive renal insufficiency.

In several reports the development of such renal damage has been attributed to the administration of ACTH or cortisone. It should be noted, however, that this complication had been observed before the introduction of these agents. Three patients in the present series had received neither ACTH nor cortisone. It is not yet clear, therefore, whether these hormones have induced such renal changes or accelerated the progression of already existing lesions.

Discussion.—DR. WILLIAM H. KAMMERER (*New York, N.Y.*): What were the dosage ranges of hormones used in these patients?

DR. RODNAN: Usually fairly moderate dosages, in the neighbourhood of 50 to 100 mg. cortisone daily. Some patients had received ACTH for only a few days, a matter of perhaps three or four injections in all.

DR. THEODORE B. BAYLES (*Boston, Mass.*): The thing that fascinates me in such patients is why you can follow them for 7, 10 or 12 years and then within 3 months develop this picture of malignant hypertension and death. Prognostically speaking, it is very important to watch for such a development, though I do not know what you can do about it.

Not so many of our scleroderma patients died of renal failure, and during these long years of observation there has been very little evidence of renal disease. The mechanism of the terminal events is most interesting.

Experiences with a New Macroscopic Test for Systemic Lupus Erythematosus. By STANLEY L. LEE, *New York, N.Y.*

The "L.E." cell phenomenon has proved a useful tool in the diagnosis of systemic lupus erythematosus, and may furnish a key to understanding the pathogenesis of this and possibly other rheumatic diseases. However, prolonged scanning of microscopic slides is tiresome and sometimes unsatisfactory in clinical work. Quantitation of the phenomenon is generally unsatisfactory, so that investigative work is hampered.

In the presence of high concentrations (0·2-0·4 mg./ml.) quinacrine hydrochloride and a protein-rich medium (*i.e.* normal serum, bovine albumin) a suspension of human leucocytes (normal or leukaemic) undergoes spontaneous agglutination. This agglutination is inhibited by serum containing the L.E. cell factor (LECF). The leucocyte-agglutination inhibiting factor (LAIF) is identical with the L.E. cell factor. It is possible, by diluting an active serum progressively with normal serum or with serum albumin, to titrate the LAIF. Some sera exhibiting LECF activity fail to inhibit leucocyte agglutination; such sera almost always show some LAIF potency when compared with normal serum as diluents for a strong LAIF serum. False positive reactions have occurred, but, as more experience is gained, these seem to be less frequent; no serum which

failed to produce L.E. cells has shown LAIF activity on two successive tests.

The test is easy to set up. As many as twenty tests have been done simultaneously, and reading is no more difficult than reading red cell agglutination tests. It is hoped that it may be useful in diagnosis and investigation.

Serum Complement Titres in the Differential Diagnosis of "Collagen Diseases" and their Aetiological Implication. By RALPH J. WEDGWOOD, *Cleveland, Ohio.*

Serum complement titres on over 300 samples from ninety patients with a variety of so-called "collagen diseases" indicate that the group can be divided into two distinct classes:

(1) Patients with acute post-infectious haemorrhagic glomerulonephritis, childhood nephrosis, and disseminated lupus erythematosus, who invariably have titres considerably below normal;
(2) Patients with rheumatoid arthritis or dermatomyositis during the active phase, who have elevated titres.

In addition, patients with chronic, subacute, or latent nephritis and with anaphylactoid purpura (Henoch-Schonlein's or Osler's syndrome), with or without renal involvement, tend to have titres higher than those of normal, healthy subjects. With induced or natural remissions, titres return towards normal ranges.

Thus the serum complement titre may be of assistance in the differential diagnosis of these diseases. Technically, the procedure is not complex, certainly no more difficult than the sheep cell differential agglutination titre; and it is readily adaptable to the routine of most laboratories performing serologic procedures.

The low complement titres in some of these diseases lead to interesting speculation. The relationship of complement to antigen-antibody interaction *in vitro* is well known; and there is experimental evidence suggesting that a similar interaction occurs *in vivo* in experimental serum sickness. While this could explain the low titres, the raised titres are more difficult to interpret. Evidence suggests that such titres occur following stress and can be induced by the injection of ACTH into an experimental animal.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md*): We are increasingly interested in finding a test or a pathological lesion that will help distinguish lupus erythematosus from rheumatoid arthritis and thus inform us which preceded the other, or whether one is a natural transition from the other. At the moment, I do not know of any single feature that is always present in one disease and not in the other, and this holds true now for the subcutaneous nodule and the sheep cell agglutination test, even when done by the Ziff euglobin modification. I wonder if Dr. Wedgwood has had any experience with this group of rheumatoid patients who also had the L.E. phenomenon so far as complement-fixation testing was concerned.

DR. WEDGWOOD: The only patient we have had was the one with dermatomyositis, and in that case the complement-fixation test came within normal limits.

Clinical Behaviour of the Haemagglutination Test for Rheumatoid Arthritis. By GIDEON K. DEFOREST, and PAUL L. BOISVERT, *New Haven, Conn.*

This paper presents the results of a modification of the haemagglutination test in 135 patients with rheumatoid arthritis, and in a group of 219 controls. The method employs the settled pattern of sheep red cells for the determination of endpoint. A positive test is a serum titre of 8 units or more.

109 (95 per cent.) of the 115 patients with classical peripheral rheumatoid arthritis in Stages 1, 2, 3, and 4 had positive tests. Positive results were obtained in three of ten patients with rheumatoid spondylitis; in one of four cases of rheumatoid arthritis with psoriasis; and in three of six with juvenile rheumatoid arthritis.

Bunim has pointed out in a recent review that the haemagglutination test does not ordinarily become positive until 12 or 18 months after onset of the disease. This makes the test results in the early cases of note. Fourteen patients had tests during the first 6 months of their illness. Thirteen (92 per cent.) of these fourteen had positive tests—two within 2 months of the onset of symptoms.

Of further interest is the relation of the titre to disease activity. It is a matter of some controversy among investigators whether the titre of the test does vary with disease activity. Among the 135 patients with rheumatoid arthritis a distinct titre change was noted only in those individuals who had dramatic Grade 1 clinical remissions. This change occurred in thirteen of fifteen such patients. The test in seven of the thirteen eventually became negative.

The control groups of patients were chosen to place a maximum of stress on the selectivity of the test. Positive tests were obtained most frequently (6·5 per cent.) in the group of adults whose sera arrived at the streptococcus laboratory. The incidence of positive tests in the total control series is at this time less than 5 per cent.

Discussion.—A SPEAKER: What constitutes, in terms of dilution of the patient's serum, the lowest dilution which would be read as a positive test and what is the average dilution in most of your positives?

While working in the laboratory of Dr. George Heller, we were able to observe two individuals hospitalized for non-arthritic complaints, who developed their first joint complaints while in the hospital. Serological tests of a somewhat different nature were positive within the first 12 hours of their disease. They have been followed subsequently and have gone on to deforming arthritis.

DR. DEFOREST: Dr. Boisvert, who is the expert of this team, is here, and I will ask him to answer that question.

DR. BOISVERT: The titre that would be considered positive is 8 units; that is, a 1 : 8 dilution of the patient's serum. This is the first tube of the test.

The usual degree of positivity or average titre for patients in the active stage will run, I think, about 128 or 256 units. We do see patients with active rheumatoid arthritis with titres of 64 and even 2,048, but usually they are in the range of 128 to 512.

DR. DARRELL C. CRAIN, JR. (*Washington, D.C.*): I should like to interject a somewhat negative response

to this test. Several years ago when it was first promulgated, I co-operated with Dr. Shultz, who was here at the Institute then, in testing 125 sera, and we obtained no correlation whatsoever between the diagnosis and the result of the test.

Recently, since the test was refined, a further group of bloods (I cannot give the exact number, though it was in excess of 30), were again submitted to a similar blindfold test and no correlation between the test and the disease was obtained.

All of us, of course, are looking for something of this sort, and the previous discussor, who mentioned several early cases which were positive and then went on to direct rheumatoid arthritis, has stated an important crux of this whole test. I think if Dr. de Forest's test is to mean anything as time goes on, it will be necessary to follow these early cases and to see if the negatives persist and 10 years later have no rheumatoid arthritis, and if the positives do so too.

DR. DEFOREST: We find that our negative tests occur most commonly in old-established cases. All our negative tests, except one, have occurred in individuals who had had the disease for many, many years and whose recent illness had been stabilized for periods of 6 months or longer.

How many of the early cases we miss, I do not know, but probably not many. I am sure some of those atypical cases whose tests were negative probably have rheumatoid arthritis, though diagnostic criteria as accepted to-day would exclude them.

DR. BOISVERT: Did I understand the statement correctly about the incidence of positive and negative tests—that there was no correlation between the tests and rheumatoid arthritis or other disease?

DR. DARRELL C. CRAIN: This was in the early stages of the test, some 4 or 5 years ago, and can probably be discounted now, but it caused us to make a bad start with the tests.

More recently, most of the discrepancies have been in positive cases which have not shown a positive test, and it may be, as Dr. de Forest says, that they are long-standing cases and that something else happens to make the test negative in chronic cases.

Relationship of the Polysaccharide Content of the Euglobulin Fraction in Rheumatoid Arthritis Serum to the Agglutination of Sensitized Sheep Erythrocytes. By CHARLEY J. SMYTH and GLENN M. CLARK, *Denver, Colo.*

Recent evidence has indicated that the "euglobulin fraction" (Ziff, Brown, Badin, and McEwen, 1954) separated from the serum of patients with rheumatoid arthritis is highly specific in agglutinating sensitized sheep erythrocytes. It has also been reported (Shetlar, Payne, Bullock, Patrick, Hellbaum, and Ishmael, 1953) that the serum polysaccharides are raised in rheumatoid arthritis as well as in other diseases. The following experiments were performed in attempt to relate these two observations.

Estimation of the polysaccharide content of the euglobulin fraction of serum by the method of Shetlar, Foster, and Everett (1948) in 214 patients showed 103 cases in which the polysaccharide content was greater than 25 mg. per cent. of original sera. In 74 of these cases the same fraction was found to agglutinate sensitized sheep erythrocytes at dilution greater than 1 : 28. Of the 111 cases in which the euglobulin polysaccharides were below 25 mg. per cent. of original serum, the haemagglutination test was positive in only four.

These findings indicate that, for haemagglutination to occur, some component which can be hydrolysed to produce a colour reaction with tryptophane must be present. However, in diseases other than rheumatoid arthritis polysaccharides, which are not components of compounds which agglutinate sensitized sheep cells, may be present in the euglobulin fraction in increased amounts.

Specific evidence that polysaccharide-containing components in rheumatoid serum are concerned in the sheep cell reaction was obtained from experiments in which it was demonstrated that when haemagglutination was produced by the euglobulin fraction, there was a significant decrease in the polysaccharide content of the supernatant fluid. It is assumed that this indicates the binding to the sensitized sheep cells of a polysaccharide-containing component of the serum of patients with rheumatoid arthritis.

Discussion.—DR. HARRY BARTFELD (*New York, N.Y.*): Do you feel that the polysaccharide itself would cause agglutination?

DR. CLARK: I feel that it would not, because we have occasionally been able to separate out the polysaccharide material by a chemical method, but have as yet been unable to reproduce the test with pure polysaccharides.

DR. HARRY BARTFELD: You probably know the work of Dr. Nanna Svartz in Sweden, who treated collagen with a bacterial enzyme and obtained an agglutination reaction with sheep cells.

DR. CLARK: Yes, Dr. Svartz has been able to identify several fractions which will agglutinate sheep cells. She was also able to demonstrate, to a member of our group who visited her laboratory last summer, separation of the fraction which causes agglutination in patients with lupus erythematosus.

Dr. Heller, in his laboratory, has at least two different fractions, and we have no idea about the relative specificity of each fraction. We have used this test because it is easy to do, and it has much simpler components than any of the more specific tests.

Also, in the euglobulin test, 3 per cent. sheep cells are used (more than in other tests), and we feel that any chemical binding which might occur, might be greater quantitatively with larger amounts of sheep cells.

DR. JOHN H. VAUGHAN (*Richmond, Va*): Could you see any gross difference between the cells agglutinated in the presence or absence of this polysaccharide? see any gross difference between the cells agglutinated I believe you indicated that you had as much as 45 micrograms of polysaccharide fixed by absorption. If this is the value you found, I think you should be able to see this amount of polysaccharide in or on the cells.

DR. CLARK: The cells show no white material, but, as we run our test, we take galactose and mannose and put it into the system to make our standard curve;

we have found, as you have, that with high concentrations of galactose and mannose over the cells originally making the standard curve, the cells look more pink than red. This pink colour also develops when the cells are agglutinated by euglobin.

We run our sheep cell test to a titre of 4 so that, even in negative tests, we do not get the little button that Dr. deForest described, but a pinkish material at the bottom. We do not know that the pink colour develops from polysaccharide coating the sheep cell erythrocytes.

REFERENCES

Shetlar, M. R., Foster, J. V., and Everett, M. R. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, 67, 125.
——, Payne, R. W., Bullock, J. A., Patrick, D. R., Hellbaum, A. A., and Ishmael, W. K. (1953). *J. clin. Invest.*, 32, 1208.
Ziff, M., Brown, P., Badin, J., and McEwen, C. (1954). *Bull. rheum. Dis.*, 5, No. 2, p. 75.

Some Characteristics of the Inhibitor System for the Sensitized Sheep Cell Agglutination. By R. R. WILLIAMS, S. S. STONE, J. JENKINS, R. L. EVANS, and J. J. BUNIM, *Bethesda, Md.*

The inhibitory activity of normal plasma has been reported by Heller to reside in Cohn Fraction II, and by Ziff in a euglobulin fraction precipitated at *p*H 5·8 Γ/2 0·013. The specific inhibitory activities varied widely in a number of Fraction II preparations. Lyophilized preparations were much more active than the 16 per cent. solutions available. Curtain electrophoresis at *p*H 3·2Γ/2 0·05 revealed an activity maximum anodic side of the protein concentration maximum. 20 to 40-fold increases in activity resulted.

Inhibitory activity can be extracted from both rheumatoid and normal euglobulins at *p*H 5·8Γ/2 0·013. Electrophoretic patterns of the extracts of rheumatoid euglobulins revealed a major component of γ mobility and a smaller β component. The original euglobulins contained components of α, β and γ mobility, with a larger proportion of the β component.

Repeated extraction of rheumatoid euglobulins sometimes reveals so much of the extractable component that equilibrium is re-established several times in a series of one-hour extractions. A small but easily measurable part of an inhibitory Fraction II preparation will bind to the rheumatoid euglobulins. The part bound appears to exert most of the inhibitory activity of this protein fraction.

It is postulated that any substance which can influence the dissociation equilibrium or bind to the active euglobulin component will exert inhibitory effects. Substances which, at 10^{-3} to 10^{-4} molar concentrations, have shown inhibitory activity include ureidosuccinic acid, 5-acetic acid hydantoin, glucosamine, and glycylglycine. Numerous amino acids, peptides, sugars, and related compounds were inactive.

Discussion.—A SPEAKER: Gamma globulin here is referred to as an inhibitor. As Dr. Heller has shown, the same gamma globulin which will inhibit these tests, when coated on a non-sensitized cell, is in itself agglutinated in the same way as all the amboceptor sensitized cells are agglutinated. It was the general feeling of our group that this did not constitute demonstration of an inhibition phenomenon; that, actually, the gamma which, as you have shown, inhibits the reaction can itself, when coated on a cell, be part of an agglutination test.

DR. WILLIAMS: It is quite possible that this is a competitive inhibition. However, the fact remains that we have measured the ratio of added normal gamma globulin to the gamma globulin calculated in the rheumatoid serum at various dilutions and measured the ratio of added gamma globulin to rheumatoid gamma globulin. When we do this, we find that one molecule to every 10 or even 100 of rheumatoid, is inhibitory. That is, the patient's own gamma globulin, present in 100 times the concentration, was unable to inhibit the reaction—which a normal inhibitory gamma globulin, even in that small proportion, could inhibit.

I think there is some difference between rheumatoid and normal gamma globulin which may involve only a small portion of Cohn's Fraction II.

DR. MORRIS ZIFF (*New York, N.Y.*): It may be that the gamma globulin factor which sensitizes the tannic acid treated sheep cell does so by coating the cell on the one hand, and complexing with the agglutinator on the other. In the case of the normal, untreated sensitized cell, it may inhibit the reaction by complexing with the agglutinator but without adding to the red cell surface, perhaps because the latter is already coated with amboceptor or because the cell surface has not been altered by tannic acid treatment.

Metabolic, Hormonal, and Anti-Rheumatic Effects of Delta-1, 9-α-Fluoro Hydrocortisone. By ROGER L. BLACK, K. LEMONE YIELDING, RALPH E. PETERSON, G. DONALD WHEDON, and JOSEPH J. BUNIM, *Bethesda, Md.*

Delta-1, 9-α-fluoro hydrocortisone (delta-1-FF) is a synthetic steroid, an analogue of prednisolone, with a fluorine atom added at C^9. Animal experiments by others have indicated that administration of this hormone to adrenalectomized rats is followed by glycogen deposition in the liver 25 to 50 times greater than is produced by hydrocortisone, and by sodium retention five times greater than is produced by DOCA.

Studies on the antirheumatic, hormonal, and metabolic effects of delta-1-FF were conducted on a group of ten patients with rheumatoid arthritis and one control subject with mild osteo-arthritis. Sodium intake was limited to 1 or 2 gm. daily. Potassium chloride was supplemented in a 10 per cent. solution, increasing the total potassium intake to from 3 to 9 gm. daily. After daily administration of 2 to 6 mg. of this steroid, the patients with rheumatoid arthritis exhibited moderate subjective and objective improvement with gradual reduction in warmth, pain on motion, tenderness, and swelling of the joints during a 2 to 4-week period. The duration of therapy ranged from 1 to 4 months.

Metabolic studies were performed on six patients including the control subject. Administration of delta-1-FF was followed by prompt and marked sodium retention. Potassium excretion was increased to a variable degree in all patients studied. Nitrogen excretion was increased slightly in only two of these six patients. Calcium and phosphorus balances in two patients to whom the drug was given for 24 and 30 days

respectively showed no significant overall change; however, faecal calcium decreased and urinary calcium increased, suggesting increased calcium absorption during the administration of the new steroid. Glucose tolerance tests showed no change in four and a diabetic curve in one after 4 weeks of delta-1-FF administration.

Endogenous adrenal cortical steroid production, as measured by plasma hydrocortisone concentration and urinary output of corticosteroids and 17-ketosteroids, was promptly suppressed by 2 mg. delta-1-FF given orally to a normal female subject.

Oedema occurred in seven patients and in four of these precluded the administration of an adequate anti-rheumatic dose. Hypokalaemia occurred in six patients; the serum potassium levels were reduced to between 2·3 to 3·0 mEq. per litre, and electrocardiographic changes appeared in four patients. Elevated serum CO_2 content was noted in five patients during the period of low serum potassium. Facial rounding occurred in seven patients. Repeated gastro-intestinal series at 4 to 6-week intervals failed to reveal any peptic ulcers.

Although, milligram for milligram, delta-1-FF has an antirheumatic potency approximately five times that of prednisone, its clinical usefulness in the rheumatic diseases is severely impaired by the electrolyte imbalance it causes. Delta-1-FF is ten times more potent than prednisone in inhibiting corticotropin secretion and suppressing adrenocortical function, which may be useful in treating certain disorders of the adrenal cortex and in studying the physiological behaviour of the pituitary-adrenal axis.

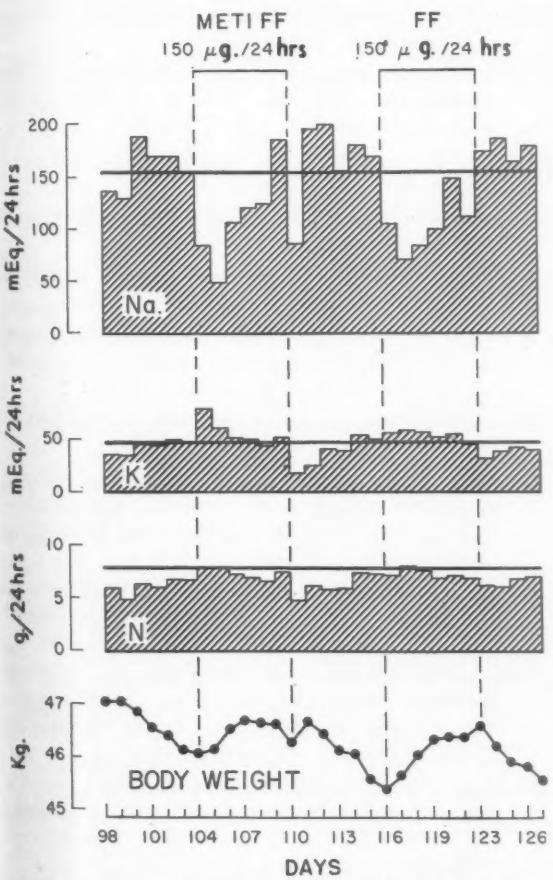


Fig. 1.—Results in a 47-year-old woman with Addison's disease.

Discussion.—DR. MAURICE PECHET (*Boston, Mass.*): We have had considerable experience in the Heart Institute for the past year with the use of delta-1-FF (originally referred to as Meti-FF). In contrast to the studies reported to-day we carried out metabolic studies in Addisonian and normal subjects on a normal dietary intake of sodium and potassium.

Fig. 1 shows the metabolic effects of Meti-FF compared directly with those of FF (9-α-fluoro hydrocortisone) in the same Addisonian subject. 150 μg. Meti-FF were administered orally daily for 6 days and after a control period 150 μg. FF were administered in a similar fashion. The sodium retention is similar in both instances. A loss of potassium occurred during the administration of Meti-FF and FF. At a dosage of 150 μg. daily there was little change in urinary nitrogen excretion.

Similar studies were carried out with normal subjects (Fig. 2). The metabolic effects associated with the oral administration of 3 mg. Meti-FF are compared with those associated with the similar administration of 3 mg. FF in the same subject. Sodium retention and increase in body weight are similar. The potassium "on-off" effect is present. On the first day of administration of the steroids there was a potassium diuresis, and on withdrawal of the steroids a retention of potassium. During the administration of Meti-FF and FF there was a considerable loss of potassium. The loss of potassium induced serum changes characteristic of hypokalaemic alkalosis. There was little change in the urinary nitrogen excretion.

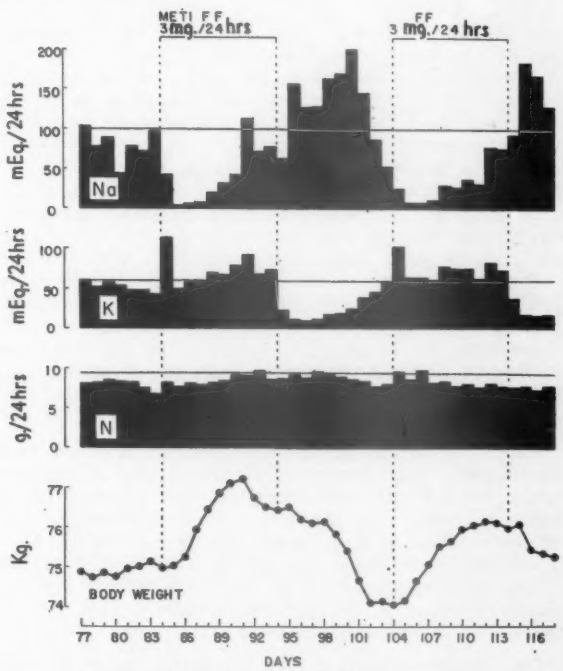


Fig. 2.—Results in a 23-year-old normal woman.

It is apparent that the magnitude of the sodium retention and potassium loss is similar for Meti-FF and FF. Meti-FF differs from FF only in possessing an extra double bond in ring A of the steroid nucleus. The introduction of the double bond in the 1,2-position of the parent steroid FF does not appreciably alter in this instance the marked sodium retaining and potassium losing properties of the parent steroid FF. Though Meti-FF and FF are valuable steroids in the treatment of Addison's disease, they are drugs which require a great deal of caution in their ordinary use.

DR. BLACK: I certainly agree with your comment. That would be our feeling about the drug, also.

DR. D. M. BERGENSTAL (*Bethesda, Md*): Dr. M. C. Li, Dr. Roy Hertz, and I have had the opportunity in the Endocrine Division of the National Cancer Institute of studying delta-1-FF for some months, and have been using doses of 2 to 10 mg. a day much higher than those reported by Dr. Black. We were trying to suppress pituitary ACTH formation enough to produce medical adrenalectomy for the control of breast cancer. We were able to show, as Dr. Black has shown, that we could suppress 17-ketosteroid formation and corticosteroid formation. If, however, one continues the administration of this drug for 1 to 2 weeks, there seems to be an escape phenomena, in that the 17-ketosteroids and urinary corticosteroids begin to rise and may return to nearly normal levels. This was observed even on doses of 10 mg. of delta-1-FF a day. Thus this compound does not seem to cause a prolonged depression of adrenal function.

We were interested in its ability to maintain adrenalectomized patients in a state of good health, for it is our feeling that cortisone used to maintain an adrenalectomized patient may be converted to oestrogen and androgen and cause a relapse of the tumour. We were able to maintain an adrenalectomized patient on as little as 1 mg. delta-1-FF a day in very good clinical condition, and we feel that this amount of material would probably not be converted to oestrogen and androgen.

We have done balance studies and have confirmed the findings of Dr. Brown and the investigators at the National Heart Institute, in that it produces a marked sodium retention with an escape phenomena after 10 days or so at a time when we began to get a sodium diuresis despite the continuation of high doses. There is also a marked loss of potassium with the development of hypokalaemia and we have observed changes in the electrocardiogram indicating a hypokalaemia.

We feel that this compound is more of a nitrogen and potassium loser than 9-α-fluoro hydrocortisone, milligram per milligram, and it seems to be more potent in depressing the eosinophil count than is 9-α-fluoro hydrocortisone. As pointed out, it is a very potent drug, and should be given with great caution, watching particularly for the development of hypokalaemia.

DR. MORRIS ZIFF (*New York, N.Y.*): Why do these compounds, 9-α-fluoro hydrocortisone and prednisone, which are synthetic and presumably do not occur in the body, so much more effective than the naturally occurring compound in suppressing adrenal function? If, as is commonly believed, the serum level determines the degree of suppression of the pituitary, this makes one wonder whether it is really hydrocortisone that controls the rate of secretion of the pituitary.

DR. BLACK: This is a very interesting point, but one which I am not prepared to answer now.

PAPERS PRESENTED BY TITLE ONLY

Metabolic and Enzymatic Adaptation in Animals. By VICTOR H. AUERBACH,* *Cambridge, Mass.*

Sjögren's Syndrome: A Study of Eight Cases. By CHARLES W. DENKO* and DELBERT M. BERGENSTAL, *Chicago, Ill.*

Comparative Susceptibility to Collagenase and Trypsin of Collagen, Soluble Collagens, and Renal Basement Membrane. By ELLIS DRESNER* and MAXWELL SCHUBERT, *New York, N.Y.*

Histochemical Studies in the Skin of Man with a Type of Bio-Assay Technique for Corticosteroids with Prolonged Local Activity. By LEON GOLDMAN, *Cincinnati, Ohio.*

Effect of Salicylate and Butazolidin on Pituitary Adrenal Function in Guinea-Pigs. By THOMAS A. GOOD* and VINCENT C. KELLEY, *Salt Lake City, Utah.*

Comparative Effectiveness of Intra-Articular Prednisone, Prednisolone, and Prednisolone Esters in Arthritic Joints. By JOSEPH L. HOLLANDER, *Philadelphia, Pa.*

Syndrome of Osteo-Arthritis, Non-Articular Tenderness, Personality Disorder, and Characteristic Life Situation. By J. H. IRVINE, *New York, N.Y.*

Mechanism of Steroid Glucuronide Formation. By KURT J. ISSELBACHER, *Bethesda, Md.*

Cartilage Mucoprotein and the Diffusibility of Dyes through Cartilage. By THOMAS G. KANTOR and MAXWELL SCHUBERT, *New York, N.Y.*

Osteo-Arthrosis—"Iatrogenic Arthritis". By H. KLINEFELTER, JR., *Baltimore, Md.*

Quantitation of the "Activity" of Rheumatoid Arthritis. By JOHN LANSBURY, *Philadelphia, Pa.*

Histopathology of Synovial Membrane. By F. W. MCCOY, *Columbus, Ohio.*

Treatment of Hip-Joint Disabilities: End-Result Study of the Resection-Angulation Operation. By HENRY MILCH, *New York, N.Y.*

Effect of Complete Adrenalectomy in Rheumatoid Arthritis. By R. D. MILLER, *Pasadena, Calif.*

Clinical and Metabolic Effects of Prednisone and Prednisolone in Rheumatoid Arthritis. By DAVID H. NEUSTADT, ROBERT MCCLENDON, and F. A. OLASH, *Louisville, Ky.*

Sources of Normal Synovial Fluids. By WARD PIGMAN, DAVID PLATT,* FRANCIS PATTON, and HOWARD L. HOLLEY, *Birmingham, Ala.*

Persistent Hyperlipaemia following Injection of a Lipid Mobilizer obtained from Plasma of Cortisonized Animals and Humans. By JOSEPH SEIFTER and DAVID H. BAEDER, *Philadelphia, Pa.*

Reactions of Intra-Articular Temperature to Vasoconstriction and Vasodilatation of the Extremities. By NATHAN M. SMUKLER and RAYMOND PENNEYS, *Philadelphia, Pa.*

* Fellow of the Arthritis and Rheumatism Foundation.

Effect of Remote Inflammation on the Granuloma Pouch. By ARTHUR I. SNYDER,* *New York, N.Y.*

Specific Amelioration of Focal Myocardial Reactions to Bovine Gamma Globulin. Preliminary Observations. By OSCAR SWINEFORD, JR.* and RUDOLPH HOENE, *Charlottesville, Va.*

Effect of 9-α-Fluoro Hydrocortisone on the Electrolyte Content of the Contracting Cat Papillary Heart Muscle. A Preliminary Report. By RALPH D. TANZ, GLENN M. CLARK, and RICHARD W. WHITEHEAD, *Denver, Colo.*

Diurnal Plasma Corticoid Studies and their relation to Morning Stiffness in Rheumatoid Arthritis. By JOSEPH E. WARREN, *Pittsburgh, Pa.*

Acquisition of Increasing Resistance to Nitrogen Mustards by transforming Mononuclear Blood Cells in Tissue Culture. By LEON P. WEISS and CARLTON SMITH, *Boston, Mass.*

* Fellow of the Arthritis and Rheumatism Foundation.

BOOK REVIEWS

Splenin A in Rheumatic Fever. By A. F. Coburn, L. V. Morre, J. Wood, and M. Roberts. 1955. Pp. 87, 5 figs. Thomas, Springfield, Ill. (27*s.* 6*d.*; $4)

"The purpose of this report is . . . primarily to determine whether Splenin A exerts any anti-inflammatory action on the manifestations of rheumatic fever." The first section is an historical review, which starts with the adverse effects noted by Coburn and Pauli in 1932 after splenectomy in rheumatic fever, and proceeds to Ungar's work in traumatic shock which first postulated the presence of anti-inflammatory substances in the spleen (1945). Splenin A was assayed in guinea-pigs by measurement of the bleeding time, which was both a difficult and a lengthy procedure. More recently, since 1951, Ungar has used another method based on the inhibition of the Arthus phenomenon in guinea-pigs.

The dosage which is believed by the authors to have a suppressive effect in children with rheumatic fever is between 20,000 and 100,000 Arthus units per day. 100,000 units, corresponding to 5 mg. of high potency material (or 1 g. of low potency extract), is obtained from 100 g. spleen. Full chemical details are given of the extraction and concentration of the material which on a large scale depends on incubation of spleen powder and ascorbic acid with enough added toluene to discourage bacterial growth.

The clinical effects of Splenin A are, however, the main concern of the authors, and, to this end, there are given 47 case histories, charts of four patients, and a full-page photograph of three smiling children "taken about 6 weeks after the onset of rheumatic fever treated only with 'massive' doses of Splenin A". In the absence of any designed trial and of control material these data remain unconvincing despite or perhaps partly because of the great amount of detail given. The authors note, however, that treatment with "dimerthate", ascorbic acid with or without "Doca", and with Thephorin was ineffective, and that treatment with salicylates, cortisone, or ACTH was effective. Presumably, if Splenin A is assayed by its anti-inflammatory effect on guinea-pigs, it will in adequate dosage have some anti-inflammatory effect in man, but this remains to be proven. As the first sentence of the book states, "This is not a therapeutic study."

E. G. L. BYWATERS.

Textbook of Orthopaedic Medicine. Volume II: Treatment by Manipulation and Massage. By James Cyriax. 5th edition. 1955. Pp. 373, 112 plates, 15 figs. Cassell, London. (21*s.*)

This is a slightly enlarged version of the fourth edition which we reviewed in 1951. By comparison with its companion, Volume I: Soft Tissue Lesions, the present work is relatively concise and is much less occupied by pathological and diagnostic fantasy. Having previously noted the author's peculiar outlook, one must admit that he does a service to physiotherapy and to medicine to-day, in stressing the importance of manipulative procedures and other manual treatments. The illustrations in this book are excellent and yet it would be dangerous to apply many of them without the sympathetic hands of one thoroughly trained in orthopaedics and physiotherapy. Dr. Cyriax describes no new method, and he had no new "idea", but his practical approach in this matter is sound.

In physiotherapy departments to-day one sees too many patients connected with the extensions of the Central Electricity Authority's network. Little effort is required by the physiotherapist and none by the patient. The waste of time and of electricity in the use of refined heat, is great. One is glad to note Dr. Cyriax's more surgical approach—that of activity of, by, and for, the patient and the physiotherapist. The use of the hands (which is *chirurgical*) should be as important to members of the Chartered Society of Physiotherapy as it was in the days when the terms *massage* and *medicinal gymnastics* were more frequently invoked.

NORMAN CAPENER.

Artritis reumatoidea. By Victor M. Castro Paullier. 1955. Pp. 201, 32 figs. Libreria Hachette S.A., Buenos Aires and Montevideo. (10 Uruguayan dollars; 19*s.* 6*d.*)

In 1934 the author treated a case of pemphigus with a new hormone derived from the anterior pituitary. The disease was cured and the drug was designated the metabolic epithelial hormone. Further, the author believes that there is a close affinity between pemphigus on the one hand and rheumatoid arthritis and fibrositis on the other. The latter maladies are due to a deficient secretion from the anterior pituitary and this deficiency leads to vascular damage, etc. The proof of all this is to be found in the excellent cure-rate brought about by this metabolic epithelial hormone. Reasons for espousing this theory are to be found in the last few chapters of the book. The remaining chapters deal with some highly revolutionary ideas on the pathology and treatment of rheumatism. It is breath-taking, to say the least, to learn that neither ACTH nor cortisone are hormones. Some doctors would agree, however, with the author's belief that they are more damaging than beneficial.

PAUL B. WOOLLEY.

HEBERDEN SOCIETY

Clinical Meeting.—The following are full reports of the papers given on November 26, 1955, summaries of which appeared in the December issue (*Annals*, 1955, **14**, 446):

Spondylitis and Heart Disease.—Dr. J. Sharp (*Manchester University*) found that 25 out of a group of 788 patients attending a clinic for the investigation of cases of spondylitis had disease of the mitral or aortic heart valves. Three of these, all with pure aortic disease, appeared to be suffering from typical ankylosing spondylitis, and it was suggested that the processes in the spine and heart might be related.

In at least seven of the remainder the changes in the heart, spine, sacro-iliac, and limb joints appeared to have resulted from severe attacks of rheumatic fever. The clinical features of these seven and of twelve further patients, who were apparently suffering from the same condition, but had not been referred to the spondylitis clinic, were described. Seventeen of them had varying degrees of permanent change in limb joints of the type originally described by Jaccoud, and twelve had residual limitation of spinal movement.

Radiographically the sacro-iliac joints were frequently involved. The changes in the spine were characterized by alteration in shape and sometimes hypoplasia of the vertebral bodies, narrowing and ossification of multiple disks without vertebral osteophytosis, apophyseal joint involvement progressing to bony ankylosis, and, occasionally, ossification of spinal ligaments. In its complete form this radiographic picture was recognizably different from that of typical ankylosing spondylitis.

Deep *x*-ray therapy did not appear to be of value in such patients, but they were usually greatly helped by aspirin. The most important measures in their long-term management appeared to be the prevention and early treatment of streptococcal infections.

Delta-1 Cortisone.—Dr. H. F. West (*Sheffield*) opened a discussion on two new steroids which he preferred to call delta-1 cortisone ("prednisone") and delta-1 cortisol ("prednisolone"). The ability of delta-1 cortisone to produce suppression of the adrenal gland was approximately the same as that of a dose of cortisol equal in therapeutic potency. Dr. Oswald Savage confirmed the therapeutic effectiveness of the new substances—particularly evident in an improvement in strength of grip. In different patients they had proved to be from two to ten times as potent as cortisone. Dyspepsia was a common toxic effect, but was not invariably worse on the new steroids than on cortisone. Cases of afebrile pneumonia and staphylococcal septicaemia had occurred during treatment. Dr. M. Thompson said that in the United States haemorrhage from the upper or lower alimentary tract was a recognized danger of treatment with the new steroids. After several months of treatment the dose often had to be increased to maintain suppression of the disease, but a change to cortisone was sometimes an effective alternative to this. Dr. G. D. Kersley had found delta-1 cortisol useful in treating a case of rheumatoid arthritis with heart failure and oedema. Dr. F. Dudley Hart had been impressed by the promptness of the response to the new steroids. He felt, however, that the increased incidence of dyspepsia associated with their use outweighed the advantage of their negligible effect on sodium metabolism. Dr. A. St. J. Dixon commented on the "lift" which a patient experienced when he was transferred from cortisone to a delta compound. Dr. E. G. L. Bywaters stressed that the incidence of side-effects was the crux of the problem, and that it was too early to draw firm conclusions on this. Dr. J. J. R. Duthie was anxious about the effect on the integrity of joints of completely suppressing inflammation and thereby removing a check to their over-use.

Rheumatoid Arthritis in a Population Sample.—Prof. J. H. Kellgren (*Manchester University*) described a survey in which a sample of the general population aged 55-64 years was examined clinically, radiologically, and serologically for evidence of rheumatoid arthritis. Clinical evidence of rheumatoid arthritis was found twice as frequently in women as in men, but *x*-ray signs of rheumatoid arthritis and positive sheep cell agglutination tests were equally distributed between the sexes. In nine out of ten individuals with severe clinical rheumatoid arthritis, the diagnosis was confirmed by a positive *x* ray and/or a positive agglutination test, but with lesser degrees of clinical disease such confirmation was less usual, and there were twenty individuals with positive *x* rays and/or agglutination tests amongst the 283 who had been recorded as free from clinical evidence of rheumatoid arthritis.

The prevalence rates in this sample ranged from 1 per cent. for men and 3 per cent. for women for severe clinical rheumatoid arthritis confirmed by either *x* ray and/or agglutination test, to 11 per cent. for men and 27 per cent. for women for all grades of clinical disease including a past history of polyarthritis.

Thus precise diagnostic definition was essential for the study of comparative prevalence rates in different populations.

Population Study of Osteo-Arthritis in Females.—Dr. J. S. Lawrence (*Manchester University*) found radiological osteo-arthritis in 83 per cent. of the males and 87 per cent. of the females in a sample of persons between the ages of 55 and 64; it was multiple (more than four groups of joints affected) in 39 per cent. of males and 49 per cent. of females. Females had significantly more radiological osteo-arthritis in the distal and proximal interphalangeal joints of the fingers, in the carpo-

metacarpal joints, in the knees, and in the metatarso-phalangeal joints of the feet. Males had significantly more osteo-arthritis only in the wrists.

Two main factors appeared to be responsible for the greater prevalence of multiple osteo-arthritis in females:

(1) A factor, believed to be genetic, associated with clinical Heberden's nodes and with osteo-arthritis of the interphalangeal, metacarpo-phalangeal, and carpo-metacarpal joints of the hands, the interfacetal joints of the cervical spine, the sacro-iliac joints, and the metatarso-phalangeal joints of the feet;

(2) a second factor, possibly also genetic, and associated with obesity and with osteo-arthritis only of the weight-bearing joints.

Other causative factors—trauma, deformities, occupation, and rheumatoid arthritis played a relatively minor role in determining the osteo-arthritic joint pattern in females.

Arthritis and Psoriasis.—Dr. V. Wright (*Stoke Mandeville*) described clinical and laboratory findings in 31 cases of arthritis associated with psoriasis. In 25 patients the arthritis was of atrophic type, five had degenerative joint disease, and one had rheumatic fever. Lesions in the skin most commonly antedated the arthritis; changes in the nails came on at the same time as the joint lesions much more often than psoriasis of the skin, and tended to wax and wane in parallel with the arthritis.

At its onset the arthritis was less often polyarticular than classical rheumatoid arthritis. Although the distal interphalangeal joints were most commonly the first joints to be involved, the process did not remain confined to them, and there seemed no reason to distinguish psoriatic arthropathy as a clinical entity in which only these joints were affected. Other clinical features of atrophic arthritis associated with psoriasis were a tendency to mimic gout, a high incidence of very complete remissions, prominence of morning stiffness in the symptomatology, and a tendency to be either very severe or very mild.

Three patients presented a picture of ankylosing spondylitis together with peripheral arthritis. The differential agglutination test was negative in all but one case—suggesting that the combination of psoriasis and arthritis is more than the coincidence of two common diseases, and that the arthritis is modified by the psoriasis if not a completely distinct entity. Among the other laboratory results, the serum globulin was high in six of 22 patients, and the alkaline phosphatase was raised in fourteen. Among the five cases with osteo-arthritis there were, rather surprisingly, four with changes in the nails.

The Isolation and Some Properties of a Neutral Salt-Soluble Collagen.—Dr. D. S. Jackson (*Manchester University*) reported a new method of isolating and purifying the so-called "alkali-soluble collagen". This involved extraction of the skins of young rabbits with neutral salt solutions followed by repeated precipitation with saturated NaCl or $(NH_4)_2SO_4$.

Physico-chemical methods suggested that the particle in solution was rod-shaped, the rods aggregating to produce fibrils of 100 Å diameter having a 2,000 Å spacing, which were transformed on warming to 37° C. to fibres of 1,000-2,000 Å diameter and the typical collagen spacing of 640 Å.

Serum Proteins in Rheumatic Fever.—Drs I. Gilliland, I. Isdale, and E. M. Abd El Wahab (*Postgraduate Medical School of London*) reported their findings in an investigation of changes in the serum proteins during the course of an attack of rheumatic fever. The ratio of albumin to α_2 globulin (measured by paper electrophoresis) was low during the initial stages of the illness and rose steadily as the patient recovered. In the discussion of this paper the importance of a suitable type of apparatus for scanning the paper strips was stressed.

SOCIETÀ ITALIANA DI REUMATOLOGIA

THIRD ACQUI PRIZE, 1957

A third international competition for a prize of L. 1,000,000 for an original and unpublished medical essay dealing with the physiopathology, clinical investigation, or therapy of rheumatism and arthritis is announced by the Acqui Spa Committee.

The competition is open to all medical practitioners, Italian and foreign. The work will be judged by an international commission comprising six well-known specialists in rheumatology and a representative of the Acqui Health and Tourist Board. The prize, which may be awarded to the best entry or divided between two entries, will be paid as soon as the result is announced. The judges reserve the right to withhold the prize if entries of sufficient merit are not received.

Entries may be written in English, French, German, Italian, or Spanish, but a summary should be provided in French or Italian. Each entry should be accompanied by a motto, with a sealed envelope bearing the motto and containing the name and address of the competitor. Eight typewritten copies should be forwarded by registered post to the Azienda Autonoma di Cura di Acqui, Piemonte, Italia, *by 31 December, 1956*. Unsuccessful entries should be claimed from the Office within 30 days of the award of the prize. Participation in the competition will be held to imply acceptance of these conditions. If the competition is postponed, the same rules will apply.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

IX International Congress on Rheumatic Diseases

Toronto, June 23-28, 1957

The Programme Committee invites contributions to the scientific programme and is anxious to receive reports on current research dealing with any aspect of the rheumatic diseases. For any such projects now in progress, or being planned for the future, the Ninth International Congress in 1957 would provide an admirable forum for their presentation to the medical public.

Programme.—The following is a tentative list of the subjects upon which the programme will be based:

- Rheumatoid arthritis and its variants
- Marie-Strümpell spondylitis
- Degenerative joint disease
- Rheumatic fever
- Gout
- Arthritis due to infection
- Non-articular rheumatism
- Psychogenic rheumatism
- Diffuse diseases of collagen-containing tissues
- Osteoporosis
- Miscellaneous articular disorders, including:
  - Traumatic arthritis
  - Neurogenic arthropathy
  - Congenital abnormalities
  - New growths, etc.
  - Back pain
  - Painful shoulder
- Surgical procedures
- Rehabilitation
- Reports on therapeutic agents
- Basic studies on connective tissue
- Biochemical research.

It is the general policy of the programme committee to give approximately equal emphasis to clinical subjects and the basic sciences in the final selection of the programme.

Length of Papers.—At the plenary sessions, papers will be of 20 minutes' duration with 10 minutes for comment by *invited discussants only*.

At other sessions papers will be of 10 minutes' duration with 5 minutes for open discussion.

Deadlines for Contributions.—Those submitting papers for consideration must supply three copies of an abstract by January 1, 1957. The prospects for acceptance of any paper will be much less after that date, and even if any are accepted, there will be difficulty in ensuring its inclusion in the printed programme.

Those presenting papers by special invitation should advise the programme committee of their titles by January 1, 1957, and their abstracts should follow not later than March 31, 1957.

Abstracts.—These should be 200 to 300 words long, and three copies should be submitted in the language in which the paper is to be given. It would be helpful, if non-English abstracts were accompanied by English translations.

Official Languages.—The official languages of the congress will be English, French, German, and Spanish.

II INTERNATIONAL CONGRESS ON PHYSIOTHERAPY

New York, 1956

The second Congress of the World Confederation for Physical Therapy is being held in New York City under the auspices of the American Physical Therapy Association, from June 17 to 23, 1956. The general theme of the congress is "Health, a Strong Force for World Understanding—the Role of the Physical Therapist", which will be introduced by Howard Rusk. Among the subjects to be discussed are physiotherapy in polio vaccine field trials, cerebral palsy, prosthetics, water exercises, obstetrics, posture, rehabilitation, heat treatment, muscle function tests, and electromyography. Study visits in New York, and post-congress tours and courses are being arranged.

Enquiries should be addressed to the Chartered Society of Physiotherapy, Tavistock House, London, W.C.1.

EMPIRE RHEUMATISM COUNCIL

The Empire Rheumatism Council are organizing and manning a stand at the Royal Society of Health Exhibition at Blackpool on April 24-27, 1956. The exhibits will seek to demonstrate to medical practitioners and others, by means of notes, diagrams, and *x* rays, a general outline of current views on rheumatoid arthritis, ankylosing spondylitis, osteo-arthritis, and gout.

Ann. rheum. Dis. (1956), **15**, 84.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Rheumatic Heart Disease as a Problem of Preventive Cardiology. BIÖRCK, G. (1955). *J. chron. Dis.*, **1**, 591. 1 fig., 8 refs.

A follow-up study was carried out during 1953 on 1,540 patients out of about 4,000 who had been admitted to Malmö General Hospital, Sweden, with rheumatic fever or some other manifestation of acute rheumatism, heart disease of presumed rheumatic origin, acute nephritis, or congenital heart disease during the years 1930-50. An analysis of data derived from these patients and from the records of about 500 others who had died in the meantime was made with particular reference to the natural history of rheumatic heart disease and the possibility of its prevention.

Of the 467 cases in which a definite diagnosis of rheumatic fever had been made originally, valvular disease was present at the time of follow-up in 25 per cent.; of 227 in which a diagnosis of "rheumatic fever (uncertain)" had been made, valvular disease was present in 11 per cent.; and of 51 patients with the original diagnosis of chorea (with no other rheumatic manifestation), 33 per cent. had valvular disease. Among the 120 cases of erythema nodosum and 311 of acute nephritis studied, the incidence of heart disease was so low that it is concluded that in these conditions no prophylactic measures against its development are necessary. There was a high incidence of recurrence among the patients with definite rheumatic fever and chorea, and the higher incidence of heart disease in patients who had had several attacks clearly indicated the need for prophylaxis against recurrence. First attacks were by no means confined to childhood, as in 124 out of 467 cases of definite rheumatic fever the patient was aged between 20 and 29 years old at the onset. There was a higher incidence of valvular disease in general in females than in males, although pure aortic lesions were far commoner in males than females.

It is suggested that there are four strategic points at which the attack on rheumatic heart disease should be concentrated:

(1) adequate treatment of the first attack of acute rheumatism;
(2) the prevention of recurrences;
(3) the medical control and supervision of patients with "possible" and "potential" heart disease; and
(4) the recognition of the correct time for surgical treatment.

[This paper contains much valuable statistical information which is difficult to abstract.] *C. Bruce Perry.*

Treatment of Acute Rheumatic Carditis with Prednisone. (La terapia delle carditi reumatiche evolutive con prednisone.) CASOLO, G., DI NARDO, A., MAGGI, C. A., ORCESE, L., ZANAZZI, A., and CIAFALONI, D. (1955). *Minerva med.* (*Torino*), **2**, 33. 12 figs, 16 refs.

Prednisone (Metacortandracin) was used at the Ospedale Maggiore, Milan, in the treatment of fifteen patients [ages not stated] with well-defined rheumatic carditis, which was classified as "acute" in ten cases and "subacute" in five. Severe cardiac decompensation was present in three of the acute cases, and pancarditis in one. Antibiotic and cortisone treatment had been unsuccessful and in some cases had even aggravated the carditis. Metacortandracin was given by mouth three or four times daily in a total dosage of 30 to 40 mg. (except in two cases in which 50 mg. was given). The treatment was continued until the clinical and laboratory findings were normal or near normal, which occurred after 8 to 15 days' treatment in all but three cases, in which progress was delayed and treatment carried on for 30 to 40 days.

All the patients responded well, and the more acute the condition, the greater was the therapeutic effect. The fact that the drug was so well tolerated permitted the use of large doses in two special circumstances:

(1) in controlling the recurrence of acute cardiac symptoms following a too rapid diminution of the dosage; and
(2) in preparation for tonsillectomy.

The side-effects were slight and the damaging influence on the cardiac condition of the disturbance of water and electrolyte metabolism which frequently accompanies

cortisone therapy was absent. Within the limits imposed by the small number of cases treated and the short period of observation (80 days), these results indicate that Metacortandracin is a drug of real value in the treatment of rheumatic carditis.

[It is impossible to do justice in an abstract to this well-documented paper, which should be read in the original by those interested.] *V. C. Medvei.*

Mechanical and Myocardial Factors in Rheumatic Heart Disease with Mitral Stenosis. HARVEY, R. M., FERRER, M. I., SAMET, P., BADER, R. A., BADER, M. E., COURNAND, A., and RICHARDS, D. W. (1955). *Circulation* (*N.Y.*), **11**, 531. 12 figs, 12 refs.

The authors argue that mitral valvotomy will not improve the condition in cases of rheumatic mitral stenosis in which myocardial insufficiency resulting from the rheumatic process rather than mechanical narrowing of the valvular orifice is the predominant cause of circulatory dysfunction. In support of this view they report the findings in sixteen patients with mitral stenosis studied at Columbia University and Bellevue Hospital, New York. These patients could be divided into two distinct groups:

The first group of eight patients gave a history of almost constant, progressive disability; haemodynamic investigation showed moderate to severe pulmonary hypertension and either a low or normal cardiac output, with diminished blood-flow response during leg-exercise. In these cases mechanical block at the mitral valve was the predominant cause of dysfunction; at surgery no mitral valve admitted the tip of the index finger. After the performance of valvotomy the pulmonary pressure fell to a greater or lesser extent, both at rest and during exercise, in every patient and the pulse pressure decreased.

The eight patients in the second group gave a history of occasional complete incapacity, but with relatively asymptomatic intervals. The haemodynamic findings showed that pulmonary tension at rest was normal or but little raised (except in one case first seen in heart failure), but that during exercise two patterns of response were found in the pulmonary circulation, namely, very little increase in pulmonary arterial pressure in two cases and a sharp rise in five cases. Analysis of the total findings in this group suggested that myocardial insufficiency unrelated to mechanical obstruction was the predominant lesion in these cases. This was partially confirmed by the fact that the performance of valvotomy in two of them was ineffective.

The authors suggest that it would seem logical to insist on a demonstration of the presence of pulmonary hypertension in every candidate for the operation of mitral valvotomy. *R. S. Stevens.*

Subacute Polyarthritis in Adults: a Condition resembling Rheumatic Fever responding only to Cortisone. (Aux confins de la maladie de Bouillaud: la polyarthrite subaiguë de l'adulte. Efficacité exclusive de la cortisone.) SERRE, H., and MIROUZE, J. (1955). *Rev. Rhum.*, **22**, 429. 5 figs.

Under the name of "subacute polyarthritis of adults" the authors include a number of diseases of obscure aetiology, the salient features of which are a vagrant polyarthritis of exudative type, with remittent pyrexia. In general, infective polyarthritis, which responds to treatment with antibiotics, and rheumatic fever, which responds to salicylates, can readily be recognized, but in this communication from Montpellier the authors describe five borderline cases in which there was a febrile polyarthritis resembling one or other of these types, but which was resistant to both antibiotics and salicylates, although all five were promptly controlled by cortisone. These cases bore little or no resemblance to classic rheumatoid arthritis.

One of these cases, which resembled an infective polyarthritis, is described in detail. It occurred in a female patient aged 27 who a few days after an attack of pharyngitis developed pyrexia and polyarthralgia, which proved to be completely resistant to antibiotics and massive doses of salicylates. A few days after the onset a scarlatiniform eruption developed, followed by desquamation. There was a marked albuminuria, which cleared up later without any signs of renal damage. The administration of cortisone brought prompt subsidence of the signs and symptoms within a few hours; maintenance doses of the hormone were continued for 4 months, and the patient has remained well for a year.

In three other cases the symptoms closely resembled those of rheumatic fever, the heart being involved in one case, but all differed in being completely unaffected by salicylates. In all three cases there was a spectacular response to cortisone, and maintenance treatment for some months appeared to bring lasting cure.

Kenneth Stone.

Therapeutic Agents in Rheumatic Carditis. Comparative Effects of Acetylsalicylic Acid, Corticotropin, and Cortisone. STOLZER, B. L., HOUSER, H. B., and CLARK, E. J. (1955). *Arch. intern. Med.*, **95**, 677. 2 figs, 13 refs.

From the results of a previous study (*Amer. J. Med.*, 1954, **16**, 168; *Abstracts of World Medicine*, 1954, **16**, 320) the authors came to the conclusion that in the acute stage of rheumatic fever there seems to be no definite advantage as between treatment with aspirin, cortisone, or corticotrophin (ACTH). Of the patients included in that investigation at Warren Air Force Base Hospital, Wyoming, 128 have now been followed up for 14 months from the beginning of treatment. Of these, 52 had been treated with aspirin, and 38 each with cortisone and ACTH respectively; the patients were also given prophylactic doses of penicillin and sulphonamides, and received a low-salt diet supplemented with potassium chloride. [The fact that the patients were young men and that nearly all of them were treated early in the course of a first attack of rheumatic fever should be emphasized.]

Analysis of the results showed that cortisone appears to have a slight but definite advantage over the other two drugs in respect of the long-term results. Thus, in the cortisone-treated group significant murmurs were present in only about seven out of 38 patients (18·4 per cent.) at the end of 14 months as compared with 34·2 and

34·6 per cent. in the other two groups. Moreover, murmurs did not develop so frequently during treatment with cortisone, and when they did they disappeared more often by the end of the period of therapy. Also, the number of murmurs that disappeared between the end of treatment with cortisone and the fourteenth monthly assessment was greater than with ACTH or aspirin. Lastly, no aortic diastolic murmurs were present at the end of 14 months in the cortisone-treated group but persisted in four of those given aspirin and in one patient given ACTH. In general, all the patients did well, and although the results obtained with cortisone were slightly better than those obtained with aspirin or ACTH the authors consider that this finding needs confirmation by further and longer-term studies.

A. Paton.

Cortisone Therapy of Initial Attacks of Rheumatic Carditis. I. Clinical Data. II. Laboratory Findings. GREENMAN, L., WEIGAND, F. A., MATEER, F. M., and DANOWSKI, T. S. (1955). *Amer. J. Dis. Child.*, **89**, 426. 1 fig., bibl.

Despite the publication of many reports on the use of cortisone in acute rheumatic carditis, agreement as to its role in the prevention of residual cardiac damage is far from general. This paper from the Children's Hospital of the University of Pittsburgh reports the findings in a series of 53 children treated for an initial attack of rheumatic carditis with large doses of cortisone for various periods (usually 6 weeks) and followed up for periods ranging from 1 to 39 months [but with no control series treated by other means], two being re-treated for recurrent attacks. The ages of the children ranged from 3·9 to 15·4 years. The diagnosis was established according to the criteria of Jones, but any case in which the clinical diagnosis of endocarditis was in the least doubtful was omitted from the analysis. In all 55 attacks, carditis was present at the onset; cardiac enlargement was present in thirty of the 55 and the mitral valve was affected in 95 per cent. of the attacks, particularly in those cases in which treatment was started 6 or more weeks after the onset. Most of the patients received 300 mg. cortisone a day by mouth for 6 weeks (though the period of treatment ranged from 3 to 113 days), the dosage then being gradually reduced over a period of 2 weeks. Treatment also included bed rest, low-salt diet (2·5 to 10 mEq. sodium with 150 mEq. potassium daily), penicillin, and digitalis or other drugs as necessary for heart failure. There were two deaths in the series. Hypertension was troublesome in two cases and treatment had to be stopped in one case because of toxic psychosis, from which the patient recovered. The authors conclude that this regimen is relatively safe and consider that its application in these cases prevented and reduced the incidence of clinically recognizable cardiac abnormalities. [It is not clear on what evidence this conclusion is based.]

The laboratory findings in this series are described in the second part of the paper. During sixteen of the 55 attacks β-haemolytic streptococci were isolated from the nasopharynx despite prophylactic penicillin therapy (100,000 units by mouth three times a day between meals), but there were no accompanying symptoms or rise in antistreptolysin-O titre. Comprehensive haematological and biochemical investigations were performed, but apart from mild hypochloraemic alkalosis no abnormality attributable to the treatment was detected, the regimen being well tolerated by the majority of the patients.

E. G. L. Bywaters.

Radiological Diagnosis of Silent Rheumatic Carditis originating in Childhood. (Die Röntgendiagnostik der im Kindesalter auftretenden symptomarmen rheumatischen Karditis.) RADNÓTI-RECHT, I., and HELL, F. (1955). *Mschr. Kinderheilk.*, **103**, 274. 13 refs.

It frequently happens that a history of rheumatic fever cannot be obtained in patients suffering from rheumatic heart disease: yet the recognition of rheumatic carditis is of obvious importance. From their experience at the Xth District Paediatric Hospital, Budapest, the authors suggest two radiological methods which they have found of diagnostic value in such cases:

The first is screening of the heart for signs of left auricular dilatation; this is best seen on turning the patient through 70° to the left while barium is present in the oesophagus.

The second sign is failure of the cardiac silhouette to become smaller on performance of Valsalva's manoeuvre. The latter procedure is possible in young patients from the age of 6 years, and the authors state that holding the breath in deep inspiration for a few seconds is sufficient.

On examination of 175 [the summary speaks of 178] children thought to be suffering from rheumatic carditis but with few or no symptoms 24·5 per cent. showed left auricular dilatation and 21 per cent. a positive result in the Valsalva manoeuvre, while both signs were present in 33·6 per cent. In contrast neither sign was observed in any of 200 children without carditis who were examined as a control. The authors suggest that the presence of either sign is good evidence in favour of active carditis, but that the absence of either does not exclude the possibility of carditis.

F. Starer.

Sydenham's Chorea. I. Evidence of Abnormal Adrenal Cortex Function. II. Effects of Hormone Therapy. AINGER, L. E., ELY, R. S., DONE, A. K., BRILL, A. B., and KELLEY, V. C. (1955). *Amer. J. Dis. Child.*, **89**, 575. Bibl.

In the first part of this study investigations were carried out on thirty children with Sydenham's chorea at Salt Lake City County Hospital (University of Utah), in an attempt to confirm the presence of abnormal adrenocortical function by means of serum assays of various substances. It was found that there was occasional elevation of the serum mucoprotein and hexosamine levels, and that the level of the serum non-glucosamine polysaccharides was consistently elevated. The plasma levels of 17-hydroxycorticosteroids were generally low, while the endogenous corticotrophin level was usually high. It is suggested that these last two findings taken together indicate relative adrenocortical deficiency. Nevertheless the plasma 17-hydroxycortico-

steroid level could be increased by the administration of ACTH, so that the adrenal glands were still capable of further activity under sufficient stimulus.

In the second part of the paper the results of hormone therapy in thirteen attacks of chorea in eleven patients (six boys and five girls) are described. ACTH was given to nine patients in doses of 2 to 4·4 units per kg. bodyweight per day, administered 6-hrly, and cortisone to two patients in doses of 7·25 to 12 mg. per kg. bodyweight per day. All but one of the patients received in addition large doses of ascorbic acid and prophylactic penicillin, and were kept at rest in bed. The duration of treatment was from 18 to 80 days. The eleven case histories are presented in detail. In five cases the response was dramatic; before treatment, two of these patients had been stuporose with severe symptoms of encephalitis and yet 3 days after treatment was begun they could feed themselves, speech became normal, and they could even walk. In five other cases marked improvement was obtained. Only one patient failed to respond and this was the patient who had received no ascorbic acid. No attempt was made to assess the benefit of treatment on the ultimate carditis.

[This almost completely successful effect of hormonal treatment of Sydenham's chorea is in direct contrast to the results reported by workers in Great Britain, for example, by Bywaters (*Arch. Dis. Childh.*, 1952, **27**, 161).]

G. S. Crockett.

Cortisone and ACTH in the Treatment of Chorea Minor. (Il cortisone e l'ACTH nella cura della corea minor.) SCHERGNA, E., and CANTARUTTI, F. (1954). *G. Psichiat. Neuropat.*, **82**, 987. 33 refs.

The treatment is described from the Univeristy Clinic for Nervous Diseases, Padua, of thirteen cases of chorea minor (Sydenham's chorea) with cortisone and ACTH (corticotrophin). Brief case histories are given of all the patients, who ranged in age from 6 to 16. The dose of cortisone was 5 to 7 mg. per kg. bodyweight and of ACTH 2 to 3 mg. per kg. daily, this being divided in the first few days of treatment into 6-hrly doses but subsequently given 12-hrly. [The choice between cortisone or ACTH for the treatment of any particular patient appears to have been made at random.]

In eleven of the patients a complete recovery was recorded within one to 2 weeks, in some cases being dramatically rapid. It was found, however, that it was only a symptomatic relief and that relapse tended to occur unless the administration of the drug was continued for a considerable time. The therapeutic background of the treatment of chorea is discussed at length, and the authors conclude that these hormones constitute a considerable advance in the treatment of chorea minor.

Donald McDonald.

Comparison of Oral Benzathine Penicillin G and Sulfonamides for the Prevention of Streptococcal Infections and Recurrences of Rheumatic Fever. MARKOWITZ, M., and HEMPHILL, W. (1955). *Pediatrics*, **15**, 509. 21 refs.

At Johns Hopkins Hospital, Baltimore, 146 children aged from 3 to 14 years who fulfilled the criteria for the diagnosis of rheumatic fever or rheumatic heart disease were studied as out-patients for periods of from 3 to 18 months (average period 13 months). One group of 82 patients (Group I) was instructed to take one tablet of 200,000 units benzathine benzylpenicillin by mouth each morning, and the remaining 64 (Group II) took 0·5 or 1·0 g. "Sulfose", a preparation containing equal parts of sulphadiazine, sulphamerazine, and sulphamethazine, the smaller dose being prescribed for children weighing less than 60 lb. (27·2 kg.). Each child was examined once a month, when throat swabs were taken and antistreptolysin-O (AS-O) titres and sedimentation rates were estimated, blood counts determined, and blood films examined.

During the period nine children developed recurrence of rheumatic fever, four in Group I and five in Group II. In eight of these cases there was an associated rise in the AS-O titre; the ninth patient gave a history of an upper respiratory infection and a Type 18 streptococcus was isolated from the throat. In each treatment group eleven children (22 in all) showed a rise in AS-O titres without developing a rheumatic relapse. In the penicillin-treated group, Group-A streptococci were isolated from the throats of fifteen, of whom eight showed a rise in AS-O titre and the other seven were considered to be carriers. In those receiving the sulphonamides Group-A streptococci were isolated from the throats of seventeen; in seven of these there was a rise in AS-O titre and the remaining ten were presumed to be carriers. Of the 82 patients taking penicillin, two developed urticarial rashes, but one was able to continue with the treatment. Toxic effects were noted in seven children in Group II; one of these had recurrent haematuria and six developed varying degrees of leucopenia, in some instances after a period of 4 to 8 months' treatment.

It is concluded that oral administration of 200,000 units benzathine benzylpenicillin is as effective as sulphonamides as a prophylactic agent in rheumatic fever and is less toxic.

C. Bruce Perry.

Successful Treatment of Beta-Hemolytic Streptococcal Infections in Children with a Single Injection of Repository Penicillin (Benzathine Penicillin G). BREESE, B. B., and DISNEY, F. A. (1955). *Pediatrics*, **15**, 516. 4 refs.

The authors report from the University of Rochester School of Medicine, Rochester, New York, the results of the treatment of 1,175 proved cases of β-haemolytic streptococcal infection in children with a single intramuscular injection of 600,000 units benzathine benzylpenicillin. The series included 944 cases of sore throat, 156 cases of scarlet fever, seventeen of otitis media, five of sinusitis, twenty of cervical adenitis, four of skin infection, eighteen of miscellaneous conditions, and eleven carriers.

In the majority of cases the infection was promptly and permanently cleared, but a number of recurrences or development of the carrier state appeared within 2 months, 8·3 per cent. with a different type of organism and 6·0 per cent. with the same type. Throat swabs

became negative one day after treatment in 76 per cent. and in 95 per cent. at the end of a week. No evidence of subsequent rheumatic fever or definite evidence of acute nephritis was observed, although one child developed transient albuminuria and haematuria. The erythrocyte sedimentation rate was raised in 14 per cent. of 664 cases tested between the second and fourth week and in 19 per cent. of 79 cases examined after the fourth week. Varying degrees of pain or discomfort at the site of the injection was the commonest untoward reaction. In 100 specially studied cases there were two cases of urticaria. The blood levels of penicillin attained by this method of treatment were never very high and indeed often proved inadequate for the treatment of deep-seated lesions, such as streptococcal cervical adenitis. However, it is claimed that in 94 per cent. of patients the infection was promptly cured and followed by no recurrence or complication. *C. Bruce Perry.*

Therapy of Acute Rheumatic Fever. DONE, A. K., ELY, R. S., AINGER, L. E., SEELY, J. R., and KELLEY, V. C. (1955). *Pediatrics*, **15**, 522. 27 refs.

In this comparative study of the effects of different treatment regimens, reported from the University of Utah College of Medicine, Salt Lake City, eighty children aged from 3½ to 15 years with acute rheumatic fever were divided into four groups:

(1) 32 were treated with ACTH in doses of 2 to 3·74 units per kg. bodyweight intramuscularly daily; these children also received 500 mg. ascorbic acid daily;

(2) Fourteen children were given cortisone either intramuscularly or orally in doses of 3 to 9 mg. per kg. body weight per day every 4 or 6 hours. In both these groups the initial dose was continued until all acute symptoms disappeared, the serum mucoprotein level showed a marked decrease, and the erythrocyte sedimentation rate (E.S.R.) had been less than 20 mm. in one hour for 3 to 5 days; the daily dose was then gradually reduced;

(3) 21 patients were treated with salicylates in doses of ⅔ to 3 grains (45 to 200 mg.) per kg. bodyweight per day at 4-hrly intervals; this dosage was continued for varying times, but in the majority until the E.S.R. had been normal for at least 8 days;

(4) Lastly, thirteen patients were treated by rest in bed alone.

The age range and the duration of symptoms before the start of treatment were similar in all four groups. In all but one child (treated by rest in bed alone) there was clinical evidence of carditis, with the development of new murmurs at the beginning of treatment.

The mean duration of joint pains in the three groups given drugs was 1·7, 2, and 3·3 days respectively, and 19·8 days in those treated with bed rest alone. The mean number of days until the E.S.R. fell to normal was respectively 15·6, 11·9, 43·4, and 48·2. Rebound phenomena on stopping treatment were observed as follows:

Two out of 28 patients receiving ACTH developed arthritis or arthralgia, three fever, and seventeen a raised E.S.R.;

Of twelve treated with cortisone, two exhibited arthralgia, four fever, and six a raised E.S.R.;

Of 21 receiving salicylates, arthritis or arthralgia was noted in seven, fever in six, and a raised E.S.R. in eight.

On discharge, persistent cardiac murmurs were present in 47 per cent. of the children treated with ACTH, 64 per cent. of those treated with cortisone, 76 per cent. of those given salicylates, and 69 per cent. of those treated with bed rest alone.

However, in those cases followed for 12 months, cardiac murmurs persisted in four out of 23 in the ACTH group, in one out of eight in the cortisone-treated group, in fourteen out of nineteen given salicylates, and in seven out of thirteen treated by bed rest.

Further, after 3 years the corresponding figures were one out of sixteen, none out of one, ten out of eleven, and four out of thirteen in the respective groups. During the 3 years follow-up new murmurs developed in three of the ACTH-treated cases, one of the cortisone-treated cases, fourteen of those given salicylates, and four of those treated by bed rest. [These figures are difficult to understand and suggest that there must have been an undue number of recurrences in the two groups of patients not treated with hormones.]

Of the patients lost to follow-up, approximately 25 per cent. of the ACTH group, 50 per cent. of the cortisone group, 90 per cent. of the salicylates group, and 71 per cent. of the bed-rest group had murmurs at their last examination.

It is concluded, despite previous reports to the contrary, that when given in adequate doses (at least 2·4 units ACTH or 6·6 mg. cortisone per kg. bodyweight a day) these hormones are of value in reducing the incidence of permanent cardiac damage in patients with rheumatic fever. *C. Bruce Perry.*

Identification of Urinary 17-Ketosteroids in Rheumatic Fever. LUBSCHEZ, R. (1955). *Pediatrics*, **15**, 537. 1 fig., 13 refs.

Since methods are now available, by the use of chromatographic separation and infra-red analysis, for identifying the major components of purified urinary 17-ketosteroid extract, and since there is some evidence that the urinary 17-ketosteroids vary qualitatively in certain diseases, the author undertook the present investigation at New York Hospital–Cornell Medical Center, New York, to determine whether there is any such qualitative change in rheumatic fever. For this purpose 24-hr specimens of urine were obtained from four non-rheumatic children, four whose rheumatism was in an inactive phase, and two with active rheumatic carditis, in one before and one during ACTH therapy. All were between the ages of 6 and 10 years.

The technique of steroid analysis is laborious, and this study was limited to the α ketosteroids. Moreover, the analytical methods were applied to 5-mg. specimens of ketosteroids (and it is therefore not surprising that of

the 35 reported α ketosteroids which have been isolated from larger specimens (50 mg.), only a few were here identified). However, the limited results obtained suggest, nevertheless, that there is no qualitative difference between the urinary ketosteroids of rheumatic and non-rheumatic children. But in the patient with active rheumatic carditis who was receiving ACTH both quantitative and qualitative differences were observed; included among the abnormal steroids in this case was one of unknown structure similar to that found by other investigators in the urine of patients with adrenal hyperplasia.

[The author stresses that this small-scale study was designed mainly to assess the possible value of a larger investigation, and is presented as a preliminary report.]

Kenneth Stone.

Studies of 17-Hydroxycorticosteroids. VII. Effects of Therapy on Concentration of 17-Hydrocorticosteroids in the Plasma of Patients with Rheumatic Fever. SEELY, J. R., ELY, R. S., DONE, A. K., AINGER, L. E., and KELLEY, V. C. (1955). *Pediatrics*, **15**, 543. 6 figs, 7 refs.

The authors have investigated at the University of Utah College of Medicine, Salt Lake City, the plasma levels of circulating adrenal steroids in patients with rheumatic fever who were being treated by bed rest alone or with cortisone, ACTH, or salicylates. Serial measurements of the concentration of 17-hydroxycorticosteroids (which includes 17-hydroxycorticosterone) in the plasma were made by the method of Nelson and Samuels (*J. clin. Endocrinol.*, 1952, **12**, 519). In the cases given hormones blood samples were obtained 4 to 5 hours after administration of one dose and just before the next was due.

In the group of nine patients treated by bed rest alone, the mean plasma steroid level was lower than the mean normal value, and a similar decreased level was found in the eight patients treated with salicylates. In the 46 patients receiving cortisone orally or lyophilized ACTH intravenously the plasma steroid levels were inconstantly elevated during the period of maximum therapy. But in the group of eleven patients receiving cortisone or ACTH gel intramuscularly, elevation of plasma steroid level was constant. Since the clinical response to the hormones, however administered, was equally satisfactory, the authors suggest that such response is not dependent upon sustained elevation of the plasma steroid level.

Kenneth Stone.

Porphyrin Metabolism. III. Urinary and Erythrocyte Porphyrin in Children with Acute Rheumatic Fever. NEVÉ, R. A., and ALDRICH, R. A. (1955). *Pediatrics*, **15**, 553. 4 figs, 32 refs.

In view of the observation of a significant increase in urinary coproporphyrin excretion in patients with rheumatic fever reported by Kapp and Coburn (*Brit. J. exp. Path.*, 1936, **17**, 255) the authors carried out a study of coproporphyrinuria, with observations on free erythrocyte porphyrins, on fifteen children with acute rheumatic fever and fifteen comparable controls at the Doernbecher Memorial Hospital for Children (University of Oregon), Portland, Oregon, the results of which are here presented.

They confirmed the earlier observations that there is a significant increase in daily excretion of this urinary pigment in all rheumatic fever patients, and that in both rheumatic and normal children the coproporphyrin is predominantly of the Type III isomer.

They found a direct correlation between urinary coproporphyrin excretion and body weight in normal children, and the correlation still held for the increased values occurring in rheumatic fever. The excretory level of the pigment was not affected by the administration of salicylates in non-toxic doses.

The erythrocyte protoporphyrin and coproporphyrin values in rheumatic fever were normal, and there appeared to be little evidence of alteration in porphyrin metabolism in the bone marrow. The liver, however, synthesizes a number of plasma constituents which present characteristic changes in acute rheumatism; among these are the serum mucoproteins. In this study the serum mucoprotein level was well above normal in all the patients with rheumatic fever, but the values returned to normal during convalescence, accompanied by a decrease in the coproporphyrinuria. The authors suggest that the liver is the source of the Type III coproporphyrin in the urine in acute rheumatism.

Kenneth Stone.

Prophylaxis against Group A Streptococci in Rheumatic Fever. The Use of Single Monthly Injections of Benzathine Penicillin G. STOLLERMAN, G. H., RUSOFF, J. H., and HIRSCHFELD, I. (1955). *New Engl. J. Med.*, **252**, 787. 15 refs.

Prophylactic injections of benzathine benzylpenicillin were given to children attending the out-patient clinic at Irvington House, New York, who had had an attack of rheumatic fever within the preceding 18 months. Between September, 1952, and August, 1954, 145 children aged 6 to 16 years each received an intramuscular injection of 1,200,000 units benzathine penicillin once a month for a total of 2,193 patient months, an average of about 20 months per patient. A further 265 patients in hospital in the acute or convalescent phase of rheumatic fever were similarly treated. The incidence of haemolytic streptococcal infection and the frequency of recurrence of rheumatic fever were compared with similar figures for a group of children treated at another hospital with penicillin by mouth or sulphadiazine.

There were no recurrences of rheumatic fever in the 145 out-patients given intramuscular injections of benzathine penicillin. In the group of 111 patients given penicillin by mouth there were two recurrences and in the groups of 73 given sulphadiazine there were five. From the patients treated with benzathine penicillin throat swabs were taken each month and cultured; only three cultures were positive for haemolytic streptococci (two of these were from the same patient at different times). One patient from whom a positive culture was obtained developed clinical pharyngitis. During the same period 52 (19·3 per cent.) of 269 untreated control children from the same environment were found to be harbouring Group-A haemolytic streptococci. Positive cultures were

obtained from throat swabs from thirteen of 99 children treated with penicillin by mouth and from eight of the 73 given sulphadiazine. Estimation each month of the serum antistreptolysin-O titre in the patients receiving benzathine penicillin revealed a significant rise in only three; in two of these there was no other evidence of streptococcal infection.

For a study of toxic reactions to intramuscular injection of benzathine penicillin the hospital patients were grouped with the out-patients, giving a total of 4,871 injections in 410 patients. Most of the patients experienced muscle soreness and tenderness for 1 to 3 days, associated in about 10 per cent. with low-grade fever for 24 to 48 hours. Urticaria was noted in four patients but this was transient and did not interfere with treatment. Various non-streptococcal infections (mainly of the upper respiratory tract and skin) occurred, and in two patients bacterial endocarditis due to *Streptococcus viridans* developed (in one case following tooth extraction).

It is concluded that single monthly injections of 1,200,000 units benzathine benzylpenicillin confer a high degree of protection against infection with Group-A haemolytic streptococci and against recurrences of rheumatic fever. *C. Bruce Perry.*

Hormonal Treatment of Acute Rheumatism with Metacortandracin. (Spunti di terapia ormonale nella malattia di Bouillaud. A proposito della nuova terapia con Metacortandracin.) SCALABRINO, R., and CURTARELLI, G. (1955). *Minerva med. (Torino)*, **1**, 1471. 10 figs, 15 refs.

The authors have used the new synthetic steroid Metacortandracin in the treatment of some twenty patients, the majority of whom were suffering from rheumatic fever. Analysis of the clinical response and results of laboratory tests showed that a daily dose of 10 to 50 mg. of the new drug was as effective as a larger dose of cortisone and produced fewer side-effects. It differs from cortisone in certain details in its action on vitamin-C metabolism. They also found the drug valuable in a case of bronchial asthma and another of pollen allergy. *L. Michaelis.*

Failure of ACTH in Acute Rheumatism as a Result of Recurrent Streptococcal Infection. (Über das Versagen von ACTH beim akuten Rheumatismus infolge rezidivierender Streptokokkeninfektionen.) PFEIFFER, E. F., and SCHÖFFLING, K. (1955). *Z. Rheumaforsch.*, **14**, 88. 1 fig., bibl.

The authors describe two cases seen at the University Medical Clinic, Frankfurt-am-Main, which illustrate the danger of hormone therapy in the presence of streptococcal infection. Both patients had rheumatic fever, with tonsillitis, and in both the administration of ACTH (corticotrophin) controlled the polyarthritis for a time. An acute exacerbation then took place in the tonsillitis and the condition of the joints relapsed once more. Antibiotics usually clear up an attack of tonsillitis very quickly, but failed to do so in these patients, even in high dosage. Evidence of cardiac damage was present in both cases.

The authors stress that in cases of acute rheumatism antibiotic treatment for associated tonsillitis should be carried out as early as possible, and if the throat infection persists tonsillectomy should be considered; it may thus be possible to avoid this particular complication of hormone therapy. In three other cases observed at the same time the tonsillitis had completely subsided before treatment with ACTH was begun and in these cases no complication was encountered. *David Preiskel.*

Prevention of First Attack Rheumatic Fever. HUBBARD, J. P. (1955). *Ann. intern. Med.*, **43**, 504. 8 refs.

Long-term Aureomycin Administration in the Prevention of Rheumatic Fever. WEINSTEIN, A. B., and KURTZ, C. M. (1955). *Wis. med. J.*, **54**, 423. 18 refs.

Case-Finding in Rheumatic Fever. WALLACE, H. M., HOENIG, L., and RICH, H. (1955). *Amer. J. Dis. Child.*, **90**, 256.

Corrected Q–T Duration in Acute and Convalescent Rheumatic Fever. CARMICHAEL, D. B. (1955). *Amer. Heart J.*, **50**, 528. 4 figs, 25 refs.

Plasma Concentrations of Vitamin A, Carotene, and Tocopherols in Rheumatic Fever during ACTH Therapy. HILLMAN, R. W., NERB, L., and HERTZ, H. (1955). *N.Y. St. J. Med.*, **55**, 2787. 23 refs.

Changes in the Electrophoresis Pattern and Antistreptolysin Titre in Rheumatic Endocarditis. (Sulle modificazioni dell'ellettroforegramma e del titolo delle antistreptolisine nel decorso della malattia di Bouillaud.) ANTONACI, B. L., and ZALAFFI, R. (1955). *Reumatismo*, **7**, 273. 14 figs, bibl.

Juvenile Rheumatism and the Danger of Rheumatism. (Über kindliches Rheuma und die Gefahren der Endokarditis.) MAI, H. (1955). *Z. Rheumaforsch.*, **14**, 273. 1 fig.

Incidence of Rheumatic Endocarditis. FASSBENDER, H. G. (1955). *Amer. Heart J.*, **50**, 537. 6 figs, 5 refs.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Rheumatoid Arthritis in Childhood. FYFE, W. M. (1955). *Glasg. med. J.*, **36**, 102. 3 figs, 8 refs.

The clinical records and the results of a follow-up investigation of 72 children (30 males and 42 females) with rheumatoid arthritis admitted to the Royal Hospital for Sick Children, Glasgow, since 1930 are reviewed. In thirty cases the age at onset of the disease was 5 years or less. The joint involvement was usually bilaterally symmetrical and muscle atrophy developed rapidly. Transient skin rashes were noted in eighteen cases and psoriasis was present in four others. Adenopathy developed in 36 cases during the illness, accompanied by

splenomegaly in ten. In five cases, two of which were fatal, there were features of both rheumatoid arthritis and rheumatic fever.

Of the 72 patients, 56 were traced, 49 of these being re-examined. The disease was quiescent—that is, there had been no joint pain and tenderness for at least 2 years—in 34 patients. Of these, 22 made a complete recovery, five were moderately crippled, five severely crippled, and two were only mildly disabled.

The value in treatment of ACTH, cortisone, vitamin D_2, gold injections, salicylates, and tonsillectomy is discussed; it is concluded that recovery is not related to any particular form of treatment given. *Kathleen M. Lawther.*

Treatment of Rheumatoid Arthritis with Cortisone. (Two- to Four-year Studies.) [In English.] HANSEN, K. B., FISCHER, F., and BRØCHNER-MORTENSEN, K. (1955). *Acta rheum. scand.*, **1**, 7. 4 figs, 15 refs.

A further study of the long-term treatment of rheumatoid arthritis with cortisone is presented from Rigshospitalet, Copenhagen, with special reference to adrenocortical activity after such treatment. The series studied consisted of fifty cases of rheumatoid arthritis in fifteen males and 35 females ranging in age from 30 to 50 years. The more severe type of case preponderated. Treatment was initiated with ACTH (corticotrophin) in order to determine the initial 17-ketosteroid excretion response, and was then continued with cortisone [presumably by mouth] at a maintenance dosage of 50 to 75 mg. daily, the level being determined by the patient's tolerance rather than by remission of symptoms. All other treatment was discontinued and the use of analgesics was avoided as far as possible.

In nineteen cases adrenocortical function was re-assessed after 9 to 41 months of continuous cortisone therapy by determining the rate of urinary excretion of 17-ketosteroids following the administration of ACTH in doses of 20 units 6-hrly. Before treatment the average increase in 17-ketosteroid excretion was 100 per cent. During treatment the average basal rate of excretion fell by 40 per cent., but stimulation with ACTH after a long period of cortisone therapy resulted in a rise in 17-ketosteroid excretion to an average of 420 per cent. of the pre-stimulation value, and 250 per cent. of the pre-treatment value. The mode of response after cortisone therapy varied, the patients falling into three groups according to the rapidity of the response, but the type of response appeared to be unrelated to age, sex, clinical condition, or dosage and duration of cortisone therapy. The decrease in adrenocortical function induced by prolonged cortisone therapy is therefore shown to be readily reversible on stimulation with ACTH.

From the clinical aspect, complete remission was induced in three cases, "considerable improvement" in nineteen cases, "some improvement" in fifteen, and none in thirteen patients. In sixteen of the fifty cases treatment was discontinued on account of an unsatisfactory response or the development of complications. Of the remaining 34 patients, the number totally incapacitated fell from eight to one, while the number of those able to work increased from two to 21. Some undesirable side-effects were noted in practically all cases. Mental disturbance occurred in eleven patients, but with no permanent damage. Two cases of gastric ulcer are recorded, and two deaths from pneumonia.

It is concluded that prolonged treatment with cortisone has proved of value in more than half the cases studied, and is indicated in cases where the disease progresses actively despite the application of other methods of control or in very active cases in order to inhibit progress before irreversible joint changes can occur. The patient should be kept continually under observation, and particular care taken to increase the dosage of cortisone rather than to stop treatment on the occurrence of infection, trauma, or acute surgical emergencies.

Harry Coke.

Two-year Trial of Combined Treatment with Cortisone and Sodium Pyrocatechol-3-carboxylate in Rheumatoid Arthritis. (Deux années d'essai de l'association cortisone-pyrocatéchol 3 carboxylate de Na, dans la polyarthrite chronique évolutive.) MICHOTTE, L. (1955). *Acta physiother. rheum. belg.*, **10**, 45. 3 refs.

The author reports the results obtained in the treatment of 25 patients (eight male and seventeen female) suffering from rheumatoid arthritis with cachets each of which contained 6 mg. cortisone and 320 mg. sodium pyrocatechol-3-carboxylate; in all but one case not more than four cachets were given daily. [The patient's ages are not stated.] Before treatment the patients were classified by the grade of the arthritis and the degree of functional impairment according to the criteria of the International League against Rheumatism, and they were similarly re-assessed at the end of 17 months.

At that time four patients had had a remission and had stopped the treatment, in two cases medication had to be interrupted as the patients developed cholecystitis and gastric ulcer respectively, while in a further six cases the treatment was abandoned in view of the poor response to the low dose of cortisone employed. The results are analysed in a table, which shows that at the beginning of treatment the numbers of patients in Grades I, II, III, and IV were respectively nil, seven, fourteen, and four, while at the end of treatment the corresponding figures were twelve, eight, four, and one.

[A large part of this paper, which might well have been better devoted to giving a more detailed account of the present series of patients, is taken up in comparing the author's results with those recorded in two series reported in the U.S.A. in which no specific treatment was used, and with the report of the American Rheumatic Association on the use of cortisone. The figures quoted from these sources seem to support the author's claim regarding the superiority of the treatment employed in his own small series.] *H. F. Reichenfeld.*

Preliminary Clinical Trials with Prednisone ("Meticorten") in Rheumatic Diseases. Comparative Antirheumatic Potency, Metabolic Activity, and Hormonal Properties. DORDICK, J. R., and GLUCK, E. J. (1955). *J. Amer. med. Ass.*, **158**, 166. 1 fig., 10 refs.

The synthetic steroid prednisone ("Meticorten";

Metacortandracin) was tried at the Beth Israel Hospital, New York City, in the treatment of twelve patients (three males and nine females, aged 35 to 63 years) suffering from active rheumatoid arthritis. The drug was usually given by mouth in a dosage of 30 mg. daily for at least 4 to 5 days until clinical improvement was observed, this being followed by gradual reduction over a period of 10 to 14 days to a maintenance dose of 5 to 20 mg. daily.

Complete remission was obtained in eight cases and major improvement in four. Within 24 hours of administration of the drug spontaneous joint pain disappeared and there was a diminution in articular and muscular stiffness. An increase in functional capacity and a reduction in the amount of joint swelling, local tenderness, and pain on movement were observed within a few days. In seven cases walking was improved. Electrolyte-balance studies revealed neither sodium retention nor potassium depletion. The antirheumatic effect of prednisone was considered to be four to five times greater than that of cortisone or hydrocortisone. Side-effects were minimal, transient, and reversible, the commonest being an increase in appetite (in eleven instances) with suppressive doses; some patients complained of insomnia and epigastric discomfort. There was no adverse change on metabolic activity.

Satisfactory results were also obtained with prednisone in systemic lupus erythematosus in a girl of 14 years and in acute gouty arthritis superimposed on chronic tophaceous gout in a man of 55. On the other hand, the drug had no effect on the rheumatic activity in a case of active rheumatic carditis. *A. Garland.*

Results of Trials of Metacortandracin in Rheumatoid Arthritis in France. (Résultats de l'expérimentation française de la Métacortandracine dans les rhumatismes inflammatoires.) COSTE, F., DELBARRE, F., MASSIAS, P., DE SÈZE, S., ROBIN, J., DEBEYRE, N., RUBENS-DUVAL, A., and LACAPÈRE, J. (1955). *Rev. Rhum.*, **22**, 385. 6 figs.

Four groups of physicians working in separate clinics in Paris have recorded in this communication their results in a trial of the new synthetic steroid Metacortandracin in the treatment of a total of 65 patients with rheumatoid arthritis or ankylosing spondylitis.

(1) Coste and his colleagues treated six patients of whom five had already been receiving hydrocortisone. A placebo was given until a relapse occurred, when Metacortandracin was substituted. These workers conclude that rheumatoid arthritis of moderate severity can be relieved by Metacortandracin as effectively as by hydrocortisone, and that this relief is obtained with much smaller doses, namely, 30 mg. daily initially, later reduced to a maintenance dose of 15 to 20 mg. daily. No evidence was found in their patients of sodium retention, in spite of an average daily intake of 7 g. sodium chloride. One patient receiving 30 mg. Metacortandracin daily developed severe melancholia which, however, gradually cleared up when the dosage was reduced.

(2) De Sèze and his colleagues treated 22 cases of rheumatoid arthritis and two of ankylosing spondylitis in patients most of whom had previously been treated with hormones for a considerable time, first with cortisone and then with hydrocortisone by mouth. In eighteen cases the disease had been fairly well stabilized by hydrocortisone, but activity still persisted in one or more joints. In most of these cases the substitution of Metacortandracin brought striking improvement which was estimated at 90 to 95 per cent. as compared with 70 to 85 per cent. improvement in response to hydrocortisone. In many of these patients the erythrocyte sedimentation rate became normal for the first time. The daily maintenance dose of Metacortandracin was 5 to 25 mg. In the remaining six patients, who were still suffering much pain despite maintenance doses of hydrocortisone, the change to 30 to 35 mg. Metacortandracin daily raised the estimated degree of improvement from 30 to 50 per cent. to one of 70 to 80 per cent. Minor signs of intolerance to hydrocortisone previously observed occurred also in response to Metacortandracin.

(3) Rubens-Duval reports eleven cases of rheumatoid arthritis, in eight of which corticoid therapy had been given for 1 to 3 years. In these eight cases the substitution of Metacortandracin was usually followed by further improvement in response to a dosage roughly one-half that of hydrocortisone or one-quarter that of cortisone. In the remaining three patients, who had had no previous hormone treatment, improvement comparable to the best results achieved with cortisone and hydrocortisone was obtained with an initial dose of 30 mg. Metacortandracin daily, reduced to a maintenance dose of 20 mg. daily.

(4) Lacapère treated 22 cases of rheumatoid arthritis and two of ankylosing spondylitis with Metacortandracin. The results were "very good" in eleven cases given a maintenance dose of 5 to 20 mg. daily, and "good" in ten. In three cases the treatment was a failure. Signs of intolerance were noted in some patients, these including signs of cardiac failure, "moon-face", gastric pain, cramp, and mental excitement.

The authors' general conclusions are that Metacortandracin has proved twice as active as oral hydrocortisone, and three times as active as cortisone. The initial dose ranged from 30 to 40 mg. daily for 5 to 10 days, after which it was progressively reduced to a maintenance dose which has varied from 15 to 25 mg. daily. The drug was in general well tolerated, but some signs of intolerance have been observed. *Kenneth Stone.*

Metacortandracin in the Treatment of Rheumatic Diseases. (La Métacortandracine dans le traitement des maladies rhumatismales.) ROBECCHI, A., DANEO, V., and MARRAZZI, G. (1955). *Rev. Rhum.*, **22**, 406. 8 refs.

At the Centre for Rheumatology, Turin, the authors have treated 38 patients with Metacortandracin for periods varying from 15 to 60 days, the initial suppressive dose being 30 to 40 mg. daily, followed by a maintenance dose of 10 to 15 mg. daily.

In 22 cases of rheumatoid arthritis a typical cortisone-like effect was constantly obtained. The activity of Metacortandracin appeared to be about five times that

of cortisone. Interruption of treatment was followed by relapse in every case, but aggravation of the initial symptoms was never seen, and when treatment was resumed it was found to be as effective as before in the same dosage. Five patients with rheumatic fever also responded well to the new steroid. Other conditions treated with success were acute peri-arthritis of the shoulder, chronic gout, bilateral arthritis of the hip associated with psoriasis, painful Heberden's nodes, and hypertrophic pulmonary osteo-arthropathy.

Minor side-effects were observed when the higher suppressive doses were given but these disappeared on reduction to the lower maintenance doses.

Kenneth Stone.

Treatment of Rheumatic Diseases with a New Synthetic Steroid: Metacortandracin. (Sul trattamento delle malattie reumatiche con un nuovo steroide di sintesi: il Metacortandracin.) ROBECCHI, A., DANEO, V., and MARRAZZI, G. (1955). *Minerva med.* (*Torino*), **1**, 1457. 7 figs, 6 refs.

The authors report the results of the administration at the Ospedale Maggiore, Turin, of Metacortandracin (Δ1:4-pregnadiene-17-α-21-diol-3:11:20-trione, "delta-cortene", prednisone) to 32 patients with various forms of acute and chronic rheumatism, among whom were 22 cases of rheumatoid arthritis of various degrees of severity. The dosage ranged from 15 to 50 mg. a day given by mouth in four equal doses. Analysis of the short-term results leads them to assess the antirheumatic activity of the drug as five times that of cortisone, while the side-effects were much rarer and less severe. Details of all cases are presented in a table and a number of graphs illustrate the clinical course in representative cases.

L. Michaelis.

Clinical Evaluation of Meticorten in Rheumatoid Arthritis and Allied Conditions. GRAY, J. W., and MERRICK, E. Z. (1955). *J. Amer. Geriat. Soc.*, **3**, 337. 2 refs.

At the Hospital of St. Barnabas, Newark, and the Orange Hospital Center, Orange, New Jersey, the synthetic steroid "Meticorten" (Metacortandracin) was given to 57 patients (including 44 between the ages of 31 and 64) with rheumatoid arthritis which had proved intractable to administration of cortisone and to other treatment. The usual dosage was 20 to 30 mg. daily. In eighteen cases there was complete remission with a normal erythrocyte sedimentation rate (E.S.R.) and no signs of joint inflammation apart from irreversible deformities, while in twenty there was major improvement with minimal residual signs. This treatment was a failure in only one case. A rapid improvement in general well-being was noted; pain and stiffness were relieved in 1 to 7 days, swelling and tenderness were reduced in 1 to 4 weeks, and the E.S.R. returned to normal in 2 weeks. The fibroelastic cellular infiltration was absorbed more completely than during any other similar treatment. Maintenance doses seemed to be more effective than safe doses of cortisone, but it was too early to decide whether "Meticorten fastness" would develop. Pain was relieved in three cases of ankylosing spondylitis and in four of osteo-arthritis of the knees and spine; there was also some relief in three cases of gouty arthritis. Side-reactions which were less prolonged and severe than with cortisone, included insomnia and nervousness, digestive disturbances, palpitation, dyspnoea, precordial oppression, weakness, facial rounding, sweating, hirsutism, and depression. The blood pressure did not change, body weight did not increase, and there was no impairment of water balance.

The authors conclude that Meticorten is four times as potent and one-quarter as toxic as cortisone.

J. N. Agate.

Effects of Prednisone ("Meticorten") on Manifestations of Rheumatoid Arthritis. Report of Early Clinical Observations. MARGOLIS, H. M., BARR, J. H., STOLZER, B. L., EISENBEIS, C. H., and MARTZ, E. W. (1955). *J. Amer. med. Ass.*, **158**, 454. 1 fig., 4 refs.

The authors report from the University of Pittsburgh the results in twenty selected cases of rheumatoid arthritis which were treated with prednisone (Metacortandracin) for periods varying from 2 weeks to 3 months. The series included early and late cases of the disease, and fourteen of them had been receiving cortisone or hydrocortisone immediately before the treatment with prednisone was begun. In the majority the maintenance dose of the drug, which was given orally, ranged between 15 and 25 mg. daily, the initial dose being between 20 and 60 mg. daily in four equal doses.

In all the patients there was an increase in functional capacity, as well as objective improvement; of sixteen cases in which the erythrocyte sedimentation rate was raised before therapy, the rate returned to normal in fourteen. The only serious side-effect was dyspepsia; there was no evidence of water retention. The authors were greatly impressed by the results achieved with prednisone in every case, though they emphasize that the period of observation was short. In an addendum to the paper they draw attention to the reported diabetogenic properties of prednisone and suggests that in future studies "this aspect of metabolism will require close scrutiny".

K. C. Robinson.

Major Undesirable Side-effects resulting from Prednisolone and Prednisone. BOLLET, A. J., BLACK, R., and BUNIM, J. J. (1955). *J. Amer. med. Ass.*, **158**, 459. 4 figs, 11 refs.

Writing from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, the authors describe in detail three cases of duodenal ulcer which occurred in a series of eighteen consecutive cases of rheumatoid arthritis treated with prednisolone or prednisone (Metacortandracin). Routine barium-meal examinations were carried out on all the patients, and in the three cases described an asymptomatic duodenal ulcer was observed to develop within a few weeks of starting the steroid therapy. In two of the cases, treatment with steroid was continued intermittently and the ulcer was seen to heal within a month with ordinary dietary and medical treatment. In the third case, in a Negro woman aged 32, the steroid was withdrawn because of the

development of a severe psychotic depression; it is noted, however, that the patient was already under psychiatric observation because of mild depression when steroid treatment was begun.

The authors emphasize the fact that the ulcers in these cases were asymptomatic and suggest the advisability of the routine administration of an aluminium hydroxide gel to patients receiving prednisone or prednisolone.

K. C. Robinson.

Treatment of Polyarthritis Chronica with Nitrogen-mustard (Erasol). [In English.] RETBOLL, G., EGEMOSE, T., and HOLSTI, J. E. (1955). *Acta med. scand.*, **151**, 289. 5 refs.

At the Town and County Hospital, Roskilde, Denmark, twelve patients suffering from rheumatoid arthritis were given intravenous injections of 0·1 mg. of "Erasol" (nitrogen mustard) per kg. body weight daily for 4 consecutive days (6 in one case). The condition of all the patients improved during treatment, though in most cases only slightly. The improvement was not maintained for more than a few weeks, however, and most patients suffered from sickness and vomiting, beginning a few hours after administration of the drug. The authors conclude that nitrogen mustard cannot be recommended for the treatment of rheumatoid arthritis except to give temporary relief in cases where other remedies have been tried and failed. *Oswald Savage.*

Treatment of Rheumatoid Arthritis with Hexamethonium Chloride: a Preliminary Report. PLATT, W. D., and STEINBERG, I. H. (1955). *Ann. intern. Med.*, **42**, 816. 19 figs.

Hexamethonium chloride was given for periods of 2 to 9 months to nine patients with active rheumatoid arthritis, three with osteo-arthritis and active rheumatoid arthritis, three with ankylosing spondylitis, and two with "pure" osteo-arthritis. The dosage of hexamethonium chloride, which was 125 mg. on the first day, was gradually increased until side-effects were produced or maximum benefit was obtained, the optimum dose usually being 375 to 500 mg. four times a day. Side-effects were observed in eleven cases. Treatment was not continuous in the patients with rheumatoid arthritis, and they were therefore observed during the withdrawal period and again during a further course of hexamethonium.

There was no evidence of any beneficial response to treatment in the patients with ankylosing spondylitis and pure osteo-arthritis, but in eight of the nine patients with rheumatoid arthritis symptomatic and functional improvement was obtained, although the general activity of the disease was unaffected. The association between rheumatoid arthritis and reflex sympathetic dystrophy is discussed and a theoretical explanation of the mode of action of hexamethonium chloride in rheumatoid arthritis is offered. *Kathleen M. Lawther.*

Pneumonia occurring during ACTH and Cortisone Therapy. JACOBS, J. H., and ROSE, F. C. (1955). *Tubercle*, **36**, 113. 5 figs, 9 refs.

In this paper from the Royal Free Hospital, London, three cases are reported in which death from pneumonia occurred during ACTH and cortisone therapy for rheumatoid arthritis.

In the first case, that of a woman aged 64 years who was admitted to hospital in a semi-comatose condition, there was no history of respiratory symptoms and examination revealed neither bronchial breathing nor adventitious sounds. Hypokalaemia was noted on admission. Death occurred on the fifteenth day despite treatment with penicillin, potassium chloride, and ACTH. Necropsy revealed generalized oedema of the lungs and lipoid infiltration of the zona fasciculata of the adrenal glands.

In the second case, that of a woman aged 61 years, there was sudden onset of cough, haemoptysis, and dyspnoea. Crepitations but no bronchial breath sounds were audible, although widespread consolidation was found at necropsy 5 days later. There was an associated monocytic leukaemia.

The third patient, a man aged 53 years, had abdominal pain and signs of consolidation at the right base on admission. He underwent laparotomy for suspected perforation because of a previous history of dyspepsia, but no perforation was found; he died 24 hours after the onset of symptoms. Necropsy revealed consolidation at the right base, degeneration of the adrenal glands with haemorrhage into one of them, and two small subacute peptic ulcers.

The authors consider that steroid therapy masked the infections, and recommend that when patients receiving ACTH or cortisone develop pneumonia the dosages of the hormones and of antibiotics should be increased.

I. Ansell.

Early Joint Lesions of Rheumatoid Arthritis. Report of Eight Cases, with Knee Biopsies of Lesions of less than One Year's Duration. KULKA, J. P., BOCKING, D., ROPES, M. W., and BAUER, W. (1955). *Arch. Path. (Chicago)*, **59**, 129. 18 figs, 28 refs.

For a study of the early joint changes in rheumatoid arthritis biopsy specimens were taken from the synovial membrane of the knee from 7 days to 9 months after the onset of clinical involvement of the joint. The clinical and histological features of the eight cases studied are described in detail. Pannus was present in only three cases. The lesions, which varied widely, are discussed under three headings:

(1) generalized proliferative inflammation with intimal hyperplasia and inflammatory cell infiltration, chiefly lymphocytes with a focal distribution;
(2) fibrin-like deposits and necrobiosis;
(3) vascular lesions, such as hyperplastic thickening of vessel walls and focal juxtavascular round-cell infiltration.

Active vasculitis was found only in the biopsy specimen taken 7 days after the onset of joint involvement. The authors state that on the whole the lesions differed from those characteristically found in the fixed joints of the later stages of rheumatoid arthritis. In the earliest stages the reaction was confined almost entirely to the intima. Lymphocytic nodules and villous hypertrophy

were seen in specimens taken more than 4 months after the onset. Some perivascular haemorrhage was also observed.

[The account of this investigation repays detailed study.] *E. G. L. Bywaters.*

Rehabilitation of the Patient with Chronic Rheumatoid Arthritis. A Two-year Study. LOWMAN, E. W. (1955). *J. chron. Dis.*, **1**, 628. 3 refs.

After briefly reviewing the incidence of and morbidity from the rheumatic diseases in the United States, the author describes an attempt made at the Goldwater Memorial Hospital, New York, to reduce disability by combining rehabilitation with medical treatment during the active phase of the disease process instead of waiting for activity to subside before starting rehabilitation. In a group of 38 patients with chronic rheumatoid arthritis, eighteen of whom were severely crippled and twenty less severely disabled, rehabilitation measures were started as soon as the maintenance dosage of cortisone or hydrocortisone had been established, the period of observation in hospital being 7 to 21 months.

Of the eighteen severely crippled patients, seven were totally self-sufficient and seven partially so when discharged; four remained in hospital. All the patients who were less severely disabled were discharged, fifteen being totally self-sufficient and five partially so. One patient in the former group and seven in the latter were able to take up full-time employment.

Kathleen M. Lawther.

Rehabilitation of the Disabled Housewife. Report of a Year's Work. HARRIS, R., and MILLARD, J. B. (1955). *Ann. phys. Med.*, **2**, 201.

Experience of the first year's working of a household training unit for disabled women at the Devonshire Royal Hospital, Buxton, is described. The unit consists of two small rooms, the larger being a twin kitchen, with two separate sinks connected respectively by a ramp to a gas and an electric cooker, and the other a "utility room" for laundry and other household tasks.

About 150 in-patients used the unit during the year, and the results obtained in 81, the majority of whom (59) had severe rheumatoid arthritis, are analysed. Before retraining, 23 of these patients were completely incapable of doing any housework, and a further 44 were capable of only light work; after retraining in household duties, kitchen methods, and work simplification, none of the 81 patients remained completely incapable, and 52 could run a normal household.

The authors comment that such a unit is cheap to instal and to run, and that since housewifery is the largest "industry" in any country, retraining of the housewife is a rewarding process. *B. E. W. Mace.*

Sulphur in Treatment of Rheumatoid Arthritis. (Le problème du soufre dans le traitement du rhumatisme chronique dégénératif.) RIZZI, M. (1955). *Acta physiother. rheum. belg.*, **10**, 117. 4 figs.

Teleradiotherapy for Rheumatoid Arthritis. (Teleroentgenterapia de la artritis reumatoidea.) ZELDIS, A., and LOPEZ, E. (1955). *Rev. argent. Reum.*, **20**, **130**. 28 refs.

Psychosocial Factors associated with Rheumatoid Arthritis. An Evaluation of the Literature. KING, S. H. (1955). *J. chron. Dis.*, **2**, 287. Bibl.

Gold Therapy in Rheumatoid Arthritis. (L'auroterapia nell'artrite reumatoide.) SCHIAVETTI, L., and FERRARIS, F. (1955). *Reumatismo*, 7, 305. 13 refs.

Treatment of Rheumatoid Arthritis with Prednisone ("Meticorten")—a Preliminary Report. MILLER, P. B. (1955). *Harper Hosp. Bull.*, **13**, 135. 5 refs.

Results of Treatment with ACTH and Cortisone in Still's Disease. (Risultati terapeutici con ACTH e cortisone nella malattia di Still-Chauffard.) MORGANO, G., RAVAZZONI, C., and FAZIO, B. (1955). *Arch. "Maragliano" Patol. Clin.*, **10**, 697. 11 figs, 9 refs.

Inhibiting Influence of Essential Hypertension on Malignant Growth and Rheumatoid Arthritis. [In English.] ZONDEK, S. G. (1955). *Acta med. scand.*, **152**, 231. 15 refs.

(Osteo-Arthritis)

Osteo-Arthritis as a Metabolic Disorder (A Statistical Study). (L'artrosi quale malattia dismetabolica. Contributo statistico.) SCARDIGLI, G. (1955). *Reumatismo*, 7, 248. 4 figs, 17 refs.

(Spondylitis)

Incidence of Leukaemia in Ankylosing Spondylitis Treated with *X* Rays. A Preliminary Report. BROWN, W. M. C., and ABBATT, J. D. (1955). *Lancet*, **1**, 1283. 10 refs.

This paper presents the preliminary findings of an investigation carried out by the authors at the Postgraduate Medical School of London under the auspices of the Medical Research Council's working party for research on leukaemia, and is based on information concerning 9,364 cases of ankylosing spondylitis treated with *x* rays at 37 radiotherapy centres in the United Kingdom. Out of 4,297 patients whose sex was recorded, 3,679 were male and 618 female, a ratio of 5·95 to 1. The age of the patients when first seen at a radiotherapy centre was noted in 2,697 cases; an age-distribution table shows that 92 per cent. of these were between the ages of 15 and 54. Information obtained from seventeen centres showed that of 3,085 patients, 1,731 (56 per cent.) were returning periodically for examination or were known to have died, while of 2,361 patients, 797 (33·8 per cent.) had more than one course of treatment.

So far, records have been obtained of 25 patients who have developed leukaemia, but this figure is likely to be incomplete as only about 44 per cent. of the 9,364

patients have been kept under observation; of these 25 patients, 21 have been certified as dying from leukaemia. In four cases ankylosing spondylitis and leukaemia were considered to co-exist when irradiation was first begun. The authors have calculated from the Registrar-General's returns for death-rates for leukaemia for the period 1940–53 that among 9,364 individuals of the same age distribution the expected number of deaths from leukaemia would be less than four. If every case in the present series were included, the ratio of observed deaths to expected deaths from leukaemia would be 5·4 to 1, while if only those cases satisfactorily followed up are included this ratio rises to 9·5 to 1.

The reported spontaneous co-existence of ankylosing spondylitis and leukaemia suggests that patients with spondylitis may have an increased susceptibility to leukaemia. This possibility is fully discussed and accepted by the authors, but after reviewing both their own evidence and that in the available literature, they come to the conclusion that *x*-irradiation plays a real part in the genesis of leukaemia. They emphasize, however, that in many cases of spondylitis radiotherapy is the only therapeutic measure which may successfully terminate a disease often characterized by great suffering and sometimes by early death. This form of treatment is therefore not necessarily contraindicated in cases of ankylosing spondylitis, provided that the diagnosis is definitely established. They suggest that repeated courses of irradiation should not be given unless absolutely necessary, as re-treatment appears to increase the likelihood of the development of leukaemia.

A. M. Jelliffe.

Fiessinger-Leroy-Reiter's Syndrome and Ankylosing Spondylarthritis; Relationship and Nosology. (Syndrome de Fiessinger-Leroy-Reiter et spondylarthrite ankylosante; parentés et place nosologique.) MARCHE, J. (1954). *Rev. Rhum.*, **21**, 321. 19 refs.

A study of 150 cases of the Fiessinger-Leroy-Reiter syndrome leads the author to state that this syndrome assumes one of the aspects of a fairly typical rheumatic disease. It is epidemiologically similar to infectious and parasitic colitis. The clinical manifestations are polymorphous. Some infection is often to be found as an initial factor. Hormonal treatment appears to be more effective than antibiotics against the rheumatic process.

S. Vallon.

C-reactive Protein Test in Ankylosing Spondylitis and in Other Rheumatic Diseases. (Il "test" della proteina C nella spondilite anchilosante ed in altre malattie reumatiche.) LUCHERINI, T., CONESTABILE, E., and NATALE, P. (1955). *Reumatismo*, **7**, 214. 3 figs, 14 refs.

In this paper from the Rheumatological Centre of the University of Rome the authors report an investigation into the value of testing for the presence of C-reactive protein in the serum of patients affected by ankylosing spondylitis and other rheumatic diseases. The technique used for the test was that of Hill (*Lancet*, 1952, **2**, 558; *Abstracts of World Medicine*, 1953, **13**, 239), in which the patient's serum reacts *in vitro* with a solution of pneumococcal C-polysaccharide.

A total of 38 cases were examined, consisting of nineteen cases of ankylosing spondylitis, four of rheumatic fever, fourteen of rheumatoid arthritis, and one of disseminated lupus erythematosus. In rheumatic fever C-reactive protein was constantly present, whereas in rheumatoid arthritis it was present only in the acute phase. In only five of the cases of ankylosing spondylitis was a positive reaction obtained, these patients being in the initial phase of the disease, when the activity of the process was indicated by severe clinical manifestations and by a high erythrocyte sedimentation rate. (The reaction was positive in the single case of disseminated lupus erythematosus studied, but this may have been due to super-added pyogenic infection.) Treatment with phenylbutazone had no effect on a positive reaction for C-reactive protein, whereas on substituting treatment with hydrocortisone the reaction rapidly became negative in many cases.

The author's conclusion is that the test for C-reactive protein is of some value in determining whether the rheumatic process is in an active or a quiescent state.

E. Forrai.

Clinical Manifestations of Spondylochondrosis (Spondylosis) of the Cervical Spine. ARNOLD, J. G. (1955). *Ann. Surg.*, **141**, 872. 11 figs, 19 refs.

In the view of the author of this paper from the University of Maryland, Baltimore, the term "spondylosis of the cervical spine" is not sufficiently descriptive and the term "spondylochondrosis" is preferable, since it takes into account both the cartilaginous protrusion and the osteophytic overgrowth of the vertebrae. In a review of the literature he points out that rupture of the intervertebral disk has been recognized as a clinical entity since the classic description of Mixter and Barr in 1934. He then describes ten cases of cervical spondylochondrosis, in seven of which the long tracts were primarily involved, with resulting paraplegia, in two the anterior roots only, producing the "anterior root syndrome", and in one both the long tracts and the anterior roots were markedly involved. The clinical and radiological findings and the treatment are described.

The author then discusses [with excellent diagrams] the anatomy of the spinal canal in the cervical region in 100 cases. The antero-posterior width of the spinal canal of the fifth vertebra was measured, and the average, both in the group as a whole and in those with normal vertebrae, was found to be 1·3 cm., the narrowest being 1 cm. and the widest 1·8 cm. It is suggested that the size of the cervical spinal canal is a significant accessory factor in the causation of symptoms in spondylochondrosis.

Discussing treatment of the condition the author states that conservative measures are of little or no value unless the lesions are minimal and non-progressive. Minimal symptoms may be present for many years and may then be followed by a fairly sudden exacerbation and marked progression; when this occurs surgical treatment should be given without delay. Laminectomy with section of

the dentate ligaments is the treatment of choice; removal of the protruding ridge of bone from the arthritic process is a hazardous procedure. Foramenotomy is indicated where the intervertebral foramen shows that it is tight around the root. The results of operation in the author's series were excellent in four cases, moderate in three, and slight in one. There was no improvement in one case and in one the condition was worse.

[This is a good paper. The author has taken a great deal of trouble, particularly in the anatomical study of the cervical spine.] *Leon Gillis.*

Genito-Urinary Infections and Ankylosing Spondylitis. (Infezioni genito-urinarie e spondilite anchilosante.) NATALE, P., and SCRIPILLITI, S. (1955). *Progr. med. (Napoli)*, **11**, 545. 3 figs, 28 refs.

Lumbar and Sciatic Pain and Spondylolisthesis. (Lombosciatalgia e spondilolistesi.) SCHIAVETTI, L., and VENANZI, S. (1955). *Reumatismo*, **7**, 299. 4 figs, 6 refs.

(Miscellaneous)

Severe and Prolonged Haematemesis in the Course of Treatment with Phenylbutazone. (Hématémèse grave et prolongée au cours d'un traitement par la phénylbutazone.) MOREAU, R., CLER, R., and PEROL, R. (1955). *Bull. Soc. méd. Hôp. Paris*, **71**, 97.

Phenylbutazone is an analgesic which has been used for the treatment of rheumatism and conditions such as osteo-arthritis. Its use, however, is sometimes accompanied by toxic side-effects, the most serious being haemorrhage from the gastro-intestinal tract. The present authors record in detail the case of a woman of 29 who had had rheumatoid arthritis as a child and occasional transitory arthritis subsequently. She had recently consulted her doctor because of a more persistent pain in the lumbar region, for which she was given phenylbutazone, a total dose of 2·9 g. being taken over a period of 5 days (250 mg. on the first day, 850 mg. on the second day, and 600 mg. for each of the 3 following days). On the second day of treatment she experienced burning epigastric pain and her stools were black. On stopping treatment the epigastric pain disappeared, but 6 days later she had a severe haematemesis and for the next 12 days her condition remained serious in spite of blood transfusions and other treatment. Radiological examination of the stomach did not establish the presence of an ulcer with any certainty. The patient eventually made a good recovery. *R. Wien.*

Use of Phenylbutazone in Rheumatoid Arthritis and Ankylosing Spondylitis. (De toepassing van butazolidine bij rheumatoïde arthritis en bij de ziekte van Bechterew.) MEYER, M. P. (1955). *Ned. T. Geneesk.*, **99**, 1546. Bibl.

The author reports the results obtained with phenylbutazone in the treatment of 161 cases of rheumatoid arthritis and von Bechterew's disease at the Rheumatism Clinic, Rotterdam. Pain was relieved in a considerable number of cases. The toxic side-effects, which were encountered in 27 per cent. of the patients (who received a dosage of 600 mg. per day later reduced to 400 or 200 mg. daily 5 days per week) were probably less frequent and less severe than with "pyramidon" (aminopyrine), but objective improvement was very seldom observed.

R. Crawford.

Diagnosis and Treatment of Reiter's Syndrome. WEINBERGER, H. J., and BAUER, W. (1955). *Med. Clin. N. Amer.*, 587. 3 figs, 4 refs.

The clinical features of an illustrative case are described, and the aetiology, differential diagnosis, and treatment are discussed.

Three cardinal points stand out in the diagnosis:

(1) The abrupt onset of urethritis, arthritis, and conjunctivitis;
(2) The repeatedly negative smears and cultures for gonococci and other pathogenic organisms; and
(3) The usually self-limiting course.

Treatment, in the absence of any definite aetiology, is empirical, and includes antibiotics, ACTH, and cortisone.

J. R. Hudson.

Osteitis Deformans (Paget's Disease) and its Ophthalmological Symptomatology. (Die Ostitis deformans Paget und ihre ophthalmologische Symptomatik.) STEMMERMANN, W. (1955). *Dtsch. med. Wschr.*, **80**, 679.

Description of the ocular symptoms of osteitis deformans–optic atrophy, papilloedema, and exophthalmos are frequent, while sclerotic macular affections, retinal haemorrhages, corneal degeneration, or cataract are less frequently found. The relationship of angioid streaks or the full Groenblad-Strandberg syndrome (angioid streaks and pseudoxanthoma elasticum) to osteitis deformans is also discussed. *W. Leydhecker.*

Reiter's Syndrome. (Sindrome de Reiter.) BERARDINELLI, W. (1954). *Med. Cirurg. Farm.*, No. 214, 61. 4 refs.

Case of Reiter's Syndrome. (Su un caso di sindrome di Reiter.) GIOMI, C., and CHIAPPARA, P. (1954). *Minerva ortop.*, **5**, 467. 4 figs, 25 refs.

Reiter's Syndrome. (La syndrome de Reiter.) FOREST, A. (1954). *Rev. Rhum.*, **21**, 517. 87 refs.

Reiter's Syndrome in Children and its Therapy. (Das Reitersche Syndrom bei Kindern und seine Therapie.) HENCKEL, H. (1954). *Z. Kinderheilk.*, **74**, 303. 1 fig., 59 refs.

Fiessinger-Leroy-Reiter Syndrome. (Le syndrome de Fiessinger-Leroy-Reiter; syndrome conjonctivo-urétero-synovial.) BOUREL, M. (1954). *Rev. Rhum.*, **21**, 249. 21 refs.

Tonsillectomy in Inflammatory Rheumatism. (L'amygdalectomie dans les rhumatismes inflammatoires.) COSTE, F., LAURENT, F., and CHEVALLIER, J. (1955). *Rev. Rhum.*, **22**, 588. 2 refs.

Significance of Tonsillectomy in the Treatment of Rheumatic Disease. (Beitrag zur Bedeutung der Tonsillektomie für die Therapie rheumatischer Erkrankungen.) SÖDRING, R. (1955). *Z. Rheumaforsch.*, **14**, 296. Bibl.

Heredity in Joint Disease. (Vererbung bei Erkrankungen der Gelenke.) STECHER, R. M., and AUSENBACHS, A. (1955). *Z. Rheumaforsch.*, **14**, 209. 11 refs.

Significance of Infections in Rheumatic Joint Disease. (Zur Bedeutung von Infektionen bei rheumatischen Gelenkkrankheiten.) WESTERGREN, A. (1955). *Wien. Z. inn. Med.*, **36**, 377. 3 refs.

Implantation of Thyroid Tissue in Chronic Articular Rheumatism. (Über Thyroidea-Implantationen beim chronischen Gelenkrheumatismus.) LAINE, V., VAINIO, K., and HOLOPAINEN, T. (1955). *Z. Rheumaforsch.*, **14**, 235. 27 refs.

Scapulohumeral Peri-Arthritis of Thoracic and Pleuropulmonary Origin. (La peri-arthrite scapulo-humerale d'origine thoracique et pleuro-pulmonaire.) RAVAULT, P., VIGNON, G., and PONSONNET, G. (1955). *Rev. Rhum.*, **22**, 421.

Tuberculous Rheumatism: a Critical Study. (Le rhumatisme tuberculeux. Étude critique.) LAYANI, F., DURUPT, L., and CHAOUAT, Y. (1955). *Rev. Rhum.*, **22**, 548. 4 figs, bibl.

Treatment of Chronic Rheumatic Diseases with Gold and Bismuth per Rectum. (Beitrag zur rektalen Gold-Wismut-Behandlung chronisch rheumatischer Erkrankungen.) HOESCH, K. (1955). *Medizinische*, No. 41, 1441. 18 refs.

An Epidemiologic Look at the Problem of Classification in the Field of Arthritis. COBB, S., MERCHANT, W. R., and WARREN, J. E. (1955). *J. chron. Dis.*, **2**, 50. 1 ref.

Disk Syndrome

Pathological Anatomy of Spondylosis Deformans. (Zur pathologischen Anatomie der Spondylosis deformans.) AUFDERMAUR, M. (1955). *Schweiz. med. Wschr.*, **85**, 827. 22 refs.

Age Distribution of the Radiological Appearances of Spondylosis Deformans. (Die Altersverteilung der Spondylosis deformans im Röntgenbild.) BECKER, R. (1955). *Z. Altersforsch.*, **9**, 72. 6 figs, bibl.

Cervical Spondylitis as a Possible Cause of Dupuytren's Contracture. (Las artrosis cervicales como posible origen de la enfermedad de Dupuytren.) BLANCO, E. M., and BROCH, F. M. (1955). *Rev. esp. Reum.*, **6**, 97. 8 figs, 14 refs.

Spondylosis; Radiological and Clinical Aspects. (Die Spondylose; Röntgenologie und Klinik.) BROCHER, J. E. W. (1955). *Schweiz. med. Wschr.*, **85**, 830.

Studies of the Radiological Appearances in so-called Rheumatic Sciatica. (Rilievi e considerazioni sul quadro radiologico della sciatica cosidetta reumatica.) DANEO, V., and MONATERI, P. C. (1955). *Reumatismo*, **7**, 239.

Gout

Action of Phenylbutazone on the Uric Acid Content of the Plasma and Erythrocytes in Relation to Clinical Phenomena. (Action de la phénylbutazone sur l'acide urique plasmatique et globulaire. Relations avec les phénomènes cliniques.) LÉVY, M., and SICHÈRE, R. M. (1955). *Rev. Rhum.*, **22**, 225. 6 refs.

There are apparently several hundred methods of determining the uric acid level in the blood, but none is entirely satisfactory. In this paper from the Hôpital Rothschild, Paris, the authors describe their own method which, if not more accurate than the others, at least has the merit of simplicity. In this the uric acid is determined by a modification of the method of Folin and Denis, first on the plasma, and then on heparinized whole blood, the object of heparinization being to prevent retraction of the erythrocytes. From these two results together with the haematocrit value the uric acid content of the erythrocyte can readily be calculated.

Using this method the authors showed that the uric acid level in the erythrocytes in a group of patients during attacks of acute gout was "remarkably high", but was not always accompanied by a rise in the plasma uric acid level. The reduction in uric acid level following administration of phenylbutazone to these patients was much more marked in the erythrocytes than in the plasma; also, in the course of the treatment the pain of acute gout often subsided simultaneously with the fall of the uric acid level in the erythrocytes.

In a group of non-gouty subjects also it was found that a high level of uric acid in the erythrocytes was often accompanied by a normal level in the plasma; some of these patients had some other form of arthralgia, while others had some metabolic disorder or migraine.

Joseph Parness.

Fate of Uric Acid in the Normal and Gouty Human Being. BUZARD, J., BISHOP, C., and TALBOTT, J. H. (1955). *J. chron. Dis.*, **2**, 42. 2 figs, 12 refs.

Substances with Anti-Rheumatic Action and with Effects on Metabolism in the Treatment of Gout. (Substances à action antirhumatismale et substances à action métabolique dans le traitement de la goutte.) BALLABIO, C. B. (1955). *Sem. Hôp. Paris*, **31**, 2723. 16 figs, bibl.

Pararheumatic (Collagen) Diseases

Acquired Circulating Anticoagulants in Systemic "Collagen Disease". Auto-immune Thromboplastin Deficiency. FRICK, P. G. (1955). *Blood*, **10**, 691. 4 figs, 22 refs.

In this paper from the University of Minnesota Hospitals, Minneapolis, the author describes the occurrence of circulating anticoagulants in three patients with

systemic collagen disease. There was evidence that two of the patients were suffering from disseminated lupus erythematosus, while the third was under observation for a drug reaction following antibiotic therapy. Circulating anticoagulants usually give rise to a haemorrhagic state with clinical features similar to haemophilia; in the present cases, however, the clinical manifestation of abnormal haemorrhage was slight in comparison with the laboratory evidence of interference with the coagulation mechanism. In one case there was transplacental passage of the anticoagulant, the latter persisting in the patient's newborn infant for 7 weeks.

The important laboratory features were similar in all three cases, and consisted in prolongation of the whole-blood clotting time and recalcification time, and defective prothrombin consumption. It was shown that the addition of a small proportion of the patients' plasma to normal plasma caused a significant lengthening of the recalcification time in the latter. Similarly the addition of the patients' plasma to normal blood caused the prothrombin consumption of the latter to become defective. These findings proved the presence of a circulating anticoagulant. Determination of one-stage clotting time showed that this too was prolonged, and in a mixture consisting of normal and patient's plasma the same phenomenon was observed.

The author concludes that the anticoagulant present in these cases acted as an antithromboplastin, and that its occurrence in association with other manifestations of hypersensitivity and the fact of its transplacental transfer suggest that the mechanism of development was immunological. A subsidiary study showed that circulating anticoagulants were present in three out of a series of thirty patients with disseminated lupus erythematosus and allied conditions, an incidence of 10 per cent. The authors have little comment to make on treatment, but suggest that prolonged administration of cortisone might have some effect, since "the effect of this drug on other types of immune antibodies like haemagglutinins has been well established".

[In most previously reported cases of circulating anticoagulants the one-stage clotting time has been normal and there has been interference only with blood thromboplastin formation. It is of considerable interest that the interference in the present cases was not only with blood thromboplastin but also with the tissue thromboplastin system, as shown by the prolongation of the one-stage clotting time.] *A. S. Douglas.*

Kidney in Lupus Erythematosus. SMITH, J. F. (1955). *J. Path. Bact.*, **70**, 41. 8 figs, 20 refs.

The renal changes in ten cases of disseminated lupus erythematosus (D.L.E.) and two cases of chronic discoid lupus erythematosus with general manifestations in the terminal illness were studied at the London Hospital. The most important histological change was considered to be the presence of Feulgen-positive, haematoxyphil bodies, and of an eosinophil, hyaline substance giving positive reactions for a basic protein to White's aniline blue-orange G stain, for arginine to Sakaguchi's test, and to the periodic-acid–Schiff test.

"Focal necrosis" involved part of the glomerular tuft in seven cases. These areas showed a background of hyaline substance with superimposed bodies of haematoxyphil material. The latter were about the size of an erythrocyte and stained purple with haematoxylin and eosin, in contrast to pyknotic nuclei, which stained blue. Capillary-loop thickening, seen in ten cases, was due to coating of the capillaries with hyaline substance smudged with haematoxyphil material. Proliferative glomerulitis was observed in eight cases and arteriolar hyaline necrosis in two only. In cases in which glomerular changes were severe there were interstitial oedema, interstitial cellular proliferation without marked fibrosis, and tubular atrophy and regeneration. In five cases there were tubular casts which gave a similar reaction to staining as the hyaline material.

As regards the histological differentiation of D.L.E. from subacute bacterial endocarditis the areas of focal necrosis in the latter do not contain haematoxyphil bodies and the eosinophil material present is fibrin, which lacks the sharp, refractile outline of the hyaline substance of D.L.E.

Capillary-loop thickening is sometimes seen in acute nephritis, eclampsia, and scleroderma, but shows no haematoxyphil smudging. Thickening due to amyloid is superficially similar, but it also involves the vasa recta (unlike D.L.E.) and may be differentiated by specific stains.

Although Klemperer's hypothesis that the source of the haematoxyphil material and hyaline substance is degraded nucleoprotein is not proven, it is, in the author's view, the only convincing explanation at present.

M. C. Berenbaum.

Therapy of Chronic Lupus Erythematosus with Synthetic Antimalarials. (O tratamento do lupus eritematoso crónico pelos antipalúdicos sintéticos.) BRANDAO, N., and DA FONSECA, A. (1955). *Act. dermo-sifiliogr.* (*Madr.*), **46**, 530. 6 refs.

Of 26 patients aged 25 to 73 suffering from chronic lupus erythematosus who were treated with synthetic antimalarials, 24 were given "Atebrin" (mepacrine) and two "Resoquin" (chloroquine) in initial doses of 200 to 500 mg. daily. Apart from two patients who are still under treatment, the other 24 were followed up for periods between one and 12 months (average 6). Re-examination showed that the lesions had completely healed and remained so in ten cases, four patients were greatly improved, four improved, two slightly improved, and three unchanged; in the remaining three patients the condition recurred at 2, 2, and 6 months respectively. A complication of treatment in the form of an exfoliative dermatitis occurred in one case, while three other patients suffered from nausea and vomiting.

Eric Dunlop.

Roentgenologic Findings in Systemic Lupus Erythematosus. An Analysis of 100 Cases. GOULD, D. M., and DAVES, M. L. (1955). *J. chron. Dis.*, **2**, 136. 5 figs, 3 refs.

A large number of cases of systemic lupus erythematosus have recently been studied at the Johns Hopkins

Hospital, Baltimore, and from these cases 100 were selected for analysis of the radiological findings. The diagnosis was established by typical clinical findings in 22 cases and histological evidence in the others.

Pleural thickening, usually present at the base of both lungs, was the most frequent abnormality, occurring in 81 cases. Massive effusion was rare. In 52 cases there were lesions in the lung parenchyma, which usually appeared as ill-defined areas of infiltration, although linear plaques were also seen in many cases. Cardiac enlargement, which was present in 53 cases, was due to pericardial effusion in only three; in the remainder it was thought to result principally from myocarditis. Although joint involvement is a prominent clinical feature of systemic lupus erythematosus the radiographs usually showed only a minimum degree of osteoporosis. Splenic enlargement, which is another clinical feature, was detected radiologically in only 34 patients.

There were a number of other incidental findings, such as impaired renal function on excretion pyelography and lung abscess due to secondary infection. The authors conclude that serial chest radiographs will demonstrate the characteristic features in most cases; they point out that even splenic enlargement was more often detected on well-exposed radiographs of the chest than on radiographs of the abdomen. *D. E. Fletcher.*

Value and Limitations of the L.E. Cell Test in the Syndrome known as Systemic Lupus Erythematosus without Skin Eruptions. [In English.] MARMONT, A. (1955). *Acta haemat.* (*Basel*), **13**, 257. 13 figs, bibl.

After a review of the literature, the author of this paper from the University of Genoa critically examines the value of the L.E.-cell test in cases of systemic lupus erythematosus without skin eruptions. He describes five such cases in which the reaction to the L.E.-cell test was positive. In the examination of these cases he found that the number of L.E. cells and rosettes increased with the severity of the disease, and that the results of tests performed with defibrinated blood were more frequently positive than those of tests with blood containing anticoagulants. Whereas with the anticoagulant technique there were no false positive reactions, with the defibrination method the clumping of neutrophil granulocytes could sometimes be confused with rosettes, and tart cells were seen which closely resembled L.E. cells. The author has observed L.E. inclusion bodies in eosinophil granulocytes. He questions whether the L.E.-cell phenomenon should be considered pathognomonic in view of the positive results occasionally obtained in patients with drug allergy. *E. G. Rees.*

Effect of Quinacrine (Atebrin) upon Lupus Erythematosus Phenomenon. DUBOIS, E. L. (1955). *Arch. Derm.* (*Chicago*), **71**, 570. 30 refs.

A method for the quantitative assay *in vitro* of the effect of mepacrine ("Quinacrine") on the L.E.-cell phenomenon is described in this paper from the University of Southern California and the County Hospital, Los Angeles. Standard solutions of the drug were mixed with potent L.E. plasma and after an interval a 20 per cent. suspension of leucocytes and some indicator of phagocytic activity, such as a solution of indian ink or a suspension of coagulase-positive staphylococci, was added. Half an hour later the mixture was examined for L.E. cells. It was found that the drug completely inhibited the L.E.-cell phenomenon at concentrations between 0·2 and 0·4 mg. per ml., depending on the potency of the original plasma. It was not leukotoxic in concentrations of less than 0·8 mg. per ml.

The author states that the highest plasma level of mepacrine that can be attained in patients taking the maximum tolerated dose is 0·1 mg. per 100 ml. However, the concentration of mepacrine in the leucocytes is 100 to 300 times the plasma level, and is well within the inhibitory range. In four patients given large doses of mepacrine the L.E.-cell phenomenon disappeared within 2 weeks; with cortisone alone 4 to 6 weeks was required to achieve the same result. It is concluded that the technique described may prove to be a valuable screening method for useful agents in the treatment of systemic lupus erythematosus. *E. G. Rees.*

Natural History of Systemic Lupus Erythematosus: an Approach to its Study through Chronic Biologic False Positive Reactors. MOORE, J. E., and LUTZ, W. B. (1955). *J. chron. Dis.*, **1**, 297. 1 fig., 11 refs.

In 1948 an investigation was begun at Johns Hopkins University and Hospital, Baltimore, the aims of which were:

(1) to investigate the validity of the treponemal immobilization (T.P.I.) test, and
(2) to study the phenomenon of "biologic false positivity".

In this paper the authors are mainly concerned with the second point, but they briefly quote the work of Zellmann, who concluded that a valid negative T.P.I. test differentiates between a syphilitic infection and a biological false positive (B.F.P.) reaction with a margin of error of about 2 per cent., provided treated early syphilis and definite clinical evidence of syphilis are excluded.

B.F.P. reactions may be "acute" or "chronic"; the acute reaction occurs shortly after an acute infectious illness, and usually disappears within 6 months. The aetiology of the chronic reaction was in 1948 almost completely unknown, but in the intervening 6 years the authors have studied 148 chronic B.F.P. reactors, of whom 104 (70 per cent.) were female. When first seen only four patients were suffering from overt disease which might have been related to the phenomenon, while of the remainder, two-thirds had no symptoms at all, and one-third had only minor symptoms which were not obviously relevant. In all cases the standard serological tests for syphilis had been positive for at least one year.

However, during the period of observation, ten patients developed definite systemic lupus erythematosus, seven developed rheumatoid arthritis (which may be the first manifestation of systemic lupus erythematosus), and 45 were tentatively diagnosed as possible or probable cases of lupus erythematosus on clinical grounds, though without pathological confirmation. The most common

clinical features of systemic lupus erythematosus, as seen in this series, are tabulated, short clinical histories of representative patients are given, and the positive laboratory findings are briefly described. Mild anaemia was fairly common in the female patients, but leucopenia was unusual. Chemical and electrophoretic tests on the serum proteins showed some abnormality of the globulin fraction in 90 per cent. of the cases. In over half the cases the erythrocyte sedimentation rate was persistently raised. It is also noted that the reaction was first observed when half the female patients and one-quarter of the males were under the age of 25. It is suggested that the finding of a B.F.P. reaction should be an indication for a search for the cause.

The clinical course of systemic lupus erythematosus developing under these circumstances appears to be exceedingly chronic, compared with the usual picture of the disease. It is hoped that continuation of this study over a further period of years will give a more accurate picture of the natural history of this disease than can be obtained from the retrospective study of advanced cases. *Nigel Compston.*

Viscero-Cutaneous Collagenosis. A Study of the Intermediate Forms of Dermatomyositis, Scleroderma, and Disseminated Lupus Erythematosus. PAGEL, W., and TREIP, C. S. (1955). *J. clin. Path.*, **8**, 1. 22 figs, 42 refs.

The close relationship between dermatomyositis and scleroderma has been recognized for some years. In scleroderma associated visceral lesions are so common that the term "progressive diffuse sclerosis" has been suggested. The present authors, writing from the Central Middlesex Hospital, London, consider that the clinical and histological features of dermatomyositis, progressive diffuse sclerosis, and disseminated lupus erythematosus, may overlap sufficiently to render differential diagnosis impossible in some cases, and they therefore suggest an even more general term—namely "viscero-cutaneous Collagenosis".

Seven cases are described in detail and excellent photomicrographs are reproduced. One patient in whom dermatomyositis was diagnosed died 11 years later from a condition in which the lesions resembled those of progressive diffuse sclerosis; it would seem that these two conditions are stages in the same disease. At necropsy on two cases clinically resembling dermatomyositis there were histological skin changes of scleroderma. In another case of scleroderma of 20 years' duration some histological changes of dermatomyositis and disseminated lupus erythematosus were found. The clinical diagnosis of polyarteritis nodosa in another case was not substantiated at necropsy, the features observed being common to disseminated lupus erythematosus, dermatomyositis, and progressive diffuse sclerosis.

The authors state that the changes in the nail fold clinically regarded as characteristic of disseminated lupus erythematosus and dermatomyositis consist in patchy extravascular fibrinoid necrosis associated with capillary thromboses—an unusual combination of collagen disease and acronecrosis. Focal necrosis and focal fibrosis respectively in the adrenal glands in two cases of dermatomyositis were considered to be early and late stages of the same process.

[For the detailed description of the histological findings in these cases the original paper should be consulted.]

Nigel Compston.

Pulmonary Lesions in Disseminated Lupus Erythematosus. PURNELL, D. C., BAGGENSTOSS, A. H., and OLSEN, A. M. (1955). *Ann. intern. Med.*, **56**, 113. 19 figs.

The gross and histological lesions in the lungs of 54 patients dying from disseminated lupus erythematosus are described in this paper from the Mayo Clinic. Secondary infection and evidence of vascular damage were found in most of the cases. No actual lesions such as "fibrinoid degeneration" were observed in the vessel walls, but in nine cases there was a curious mucinous oedema in the perivascular and peribronchial tissues with some spread into the alveolar walls. It is suggested that this may be the precursor of fibrinoid change.

A. C. Lendrum.

Multineuritic and Polyneuritic Forms of Peri-Arteritis Nodosa. (Sur les formes multinévritiques et polynévritiques de la périartérite noueuse.) GARCIN, R., GODLEWSKI, S., GRUNER, J., LAPRESLE, J., and LAMBERT, P. (1955). *Ann. Méd.*, **56**, 113. 19 figs.

The authors describe seven cases seen at the Hospice de la Salpêtrière, Paris, in which a neuritic disorder developed in the course of periarteritis nodosa. Of these, three conformed to an asymmetrical multineuritis, three showed a symmetrical polyneuritic distribution, while in the seventh case the early neurological picture was soon overshadowed by the muscular, articular, and cutaneous manifestations of the disease. Pathological confirmation was obtained by biopsy or (in three cases) at necropsy. In three of the cases the administration of ACTH or cortisone in doses of 100 mg. per day appeared to produce beneficial results, although one of the fatal cases was also treated with corticoids. (The reproduction of a photomicrograph of material obtained at one of the necropsies shows an excellent specimen of an obliterated arteriole in a spinal root.)

The special clinical features in these cases to which attention is drawn included pyrexia and constitutional disorder, loss of weight, anaemia, the presence of eosinophilia with a moderate polymorphonuclearcytosis, and a constant elevation of the erythrocyte sedimentation rate; urinary disorders, with casts, albuminuria, and microscopic haematuria, were present in most of the cases, and in one porphyrinuria occurred. Abdominal pain was prominent in four cases, and oedema also in four. The occurrence of other neurological manifestations (apart from the polyneuritis or mononeuritis multiplex) such as mental confusion (one case), fits (two cases), and coma (one case), indicate the pleomorphism of the condition. The importance of muscle biopsy for diagnostic confirmation is stressed, although it is pointed out that a negative biopsy result does not exclude absolutely the possibility of periarteritis.

L. A. Liversedge.

Pulmonary Appearances in Polyarteritis Nodosa. STRICKLAND, B. (1955). *J. Fac. Radiol.* (*Lond.*), **6**, 201. 14 figs, 14 refs.

In this paper from St. Mary's Hospital, London, the author first points out that from experiments in animals and clinical observations it would appear that polyarteritis nodosa is a manifestation of anaphylactic hypersensitivity to various antigens. Pathologically, necrotizing, inflammatory, obliterative lesions of the small arteries are widespread throughout the body. Males are more commonly affected than females and the age incidence is usually 30 to 40 years. Fever is generally present either at the onset or later in the disease. The prognosis is poor, but some patients have benefited from administration of ACTH or cortisone, although the long-term results of this form of treatment have yet to be assessed.

Radiologically, the changes seen in the lung fields —apart from terminal manifestations of heart failure, such as gross cardiac enlargement and pulmonary oedema—take the form of infiltrations of very varying pattern and sometimes of pleurisy with effusion. Six cases are briefly reported and radiographs are reproduced. The lesions tend to be transient and migratory and there may be complete clearing of the lung fields between attacks. Post-mortem examination revealed multiple granulomata and areas of necrosis in the small vessels at different stages of development. The author discusses the radiological changes in relation to eosinophilia, which was a feature in three of the cases described; he considers that some of these may be of the same nature as "eosinophilic lung", but that multiple granulomata and, to a lesser extent, infarcts and small atelectases also play a part in creating the bizarre picture. *A. M. Rackow.*

Histological Aspects of Periarteritis Nodosa. (Sur les aspects histologiques de la périartérite noueuse.) HABIB, R. (1955). *Ann. Méd.*, **56**, 352. 24 figs.

Blood 17-Hydroxycorticosteroid Levels in a Case of Acute Disseminated Lupus Erythematosus treated with "Nevaquin" (Chloroquine). (Dosage des 17-hydroxycorticosteroides sanguins dans un cas de lupus erythémateux aigu disséminé traité par Nivaquin (Chloroquine).) ROSKAM, J., CAUWENBERGE, H., and VLIERS, M. (1955). *Acta physiother. rheum. belg.*, **10**, 85. 21 refs.

General Pathology

Antimyocardial Antibodies in Rheumatic Fever. [In English.] REJHOLEC, V., and WAGNER, V. (1955). *Experientia* (*Basel*), **11**, 278. 1 fig., 6 refs.

A brief report on the quantitative estimation of autoantibodies in the serum of patients suffering with rheumatic fever, rheumatoid arthritis, and glomerulonephritis is presented from the Research Institute of Rheumatic Diseases, Prague, and Charles University, Pilsen. Organ antigens were prepared from normal human kidney, myocardium, and liver by extraction with 1·1 per cent. sodium chloride solution and the extracts used to treat collodion particles by Cavelti's method. The "sensibilized" particles were then incubated for one hour at room temperature admixed with geometric dilutions of the patient's serum and the presence of agglutination determined with an agglutinoscope. Antimyocardial antibodies were found in the serum at an average titre of 1 in 20 in six out of eight cases of rheumatic fever; at an average titre of 1 in 16 in eight out of ten cases of "acute tonsillitis showing the so-called myocardial E.C.G. curve"; and at a titre of 1 in 4 in all of three cases of rheumatoid arthritis. These antibodies were present at a low titre in the serum in most of sixteen cases of active glomerulonephritis, but in none of ten cases of latent glomerulonephritis. In a control group of 57 healthy subjects these antibodies were present at a low titre in a small number of cases. It was found that in cases of acute rheumatism the titre of antimyocardial antibodies were reduced as a result of salicylate therapy. *Harry Coke.*

Rheumatic Fever Activity Determination by Two Correlative Methods. SKILLMAN, R. K., SPURRIER, W., FRIEDMAN, I. A., and SCHWARTZ, S. O. (1955). *Arch. intern. Med.*, **96**, 51. 25 refs.

At the Hektoen Institute for Medical Research (Cook County Hospital), Chicago, the authors investigated the value of two antigen–antibody reactions as a means of determining rheumatic fever activity; the trial was carried out on 78 patients with rheumatic fever (active and inactive) and 77 controls.

In Method I the serum of rheumatic fever patients was used as the antibody and sheep erythrocytes coated with heat-killed Group-A β-haemolytic streptococci from rheumatic fever patients as the antigen, complement being then added to produce haemolysis.

In Method II Group-A β-haemolytic streptococcus antiserum from immunized rabbits was employed as antibody and the patient's erythrocytes as antigen.

Method I, using the patient's serum as the antigen source, was found to be the more sensitive and showed better correlation with the clinical state. Of the patients in whom the disease was clinically active, 98 per cent. gave a positive haemolytic reaction, as against 89 per cent. with the agglutination method. In those in whom the disease was considered inactive, the respective positive reactions were 48 and 30 per cent. The height of the titre did not indicate the severity of the process, and showed no correlation with the erythrocyte sedimentation rate. Treatment with cortisone or salicylates did not interfere with the determinations. In all the 77 control subjects the reactions were negative by both methods. It is concluded that these reactions are of practical value in assessing the activity of rheumatic fever, as well as in its diagnosis. *G. W. Csonka.*

Glycine Metabolism in Rheumatoid Arthritis and Allied Diseases. LEMON, H. M., LOONEY, J. M., and CHASEN, W. H. (1955). *Rheumatism*, **11**, 48. 3 figs, 26 refs.

The high percentage of glycine in the molecules of collagen and elastin compared with those of the other body proteins suggested to the authors that in rheu-

matoid arthritis and other diseases characterized by lesions affecting the connective tissues glycine metabolism might show some detectable disturbance. Benzoic acid being detoxified by conjugation with glycine and excreted as hippurate by the kidney, they studied the effect on the serum glycine and alanine levels and on urinary hippurate excretion of the intravenous administration of 1·77 g. sodium benzoate after a 12-hour fast to 91 non-rheumatic control subjects (some with other diseases of bones or joints), 127 patients with rheumatoid arthritis or ankylosing spondylitis, 24 with rheumatic fever or inactive rheumatic heart disease, and seven with diffuse collagen disease (disseminated lupus erythematosus or scleroderma). Tests of renal and hepatic function were carried out and all patients with gross disorders of these organs were excluded (although 16 per cent. of the patients studied had albuminuria and 20 per cent. had minor defects of hepatic function as shown by the "bromsulphophthalein" excretion test or determination of plasma protein partition).

Comparison of the fall in serum glycine levels following the administration of sodium benzoate in the various groups revealed a considerable overlap between the values obtained for the non-rheumatic and rheumatic cases, while even in the same individual marked variations occurred which did not correlate closely with changes in the clinical condition or the erythrocyte sedimentation rate. Statistically significant differences were demonstrated, however, which "can be interpreted best as indicative of reduced reservoirs of readily available glycine in the rheumatoid state, particularly when clinically active disease is present". No such correlation was found between rheumatoid activity and the changes in the serum alanine level or urinary hippurate excretion.

R. E. Tunbridge.

Clot Density Determination of Fibrinogen in Rheumatic Fever. LOSNER, S., VOLK, B. W., and KANOF, A. (1955). *Amer. Heart J.*, **50**, 100. 7 figs, 28 refs.

In 33 cases of rheumatic fever and six cases of rheumatic heart disease without active rheumatism studied at the Jewish Chronic Disease Hospital, Brooklyn, New York, the plasma fibrinogen level was estimated at frequent intervals and compared with the erythrocyte sedimentation rate (E.S.R.). The latter was determined by Wintrobe's method, and the former by the spectrophotometric measurement of the increase in optical density of the plasma during clotting. In addition, tests for the presence of C-reactive protein (C.R.P.) were carried out at least once in every case.

An increase in the plasma fibrinogen level was found only when there was clinical evidence of active rheumatism, and was sustained only in cases with a protracted clinical course. The level remained normal in cases in which an elevated E.S.R. was unaccompanied by other evidence of activity and in cases of inactive rheumatic heart disease complicated by respiratory infection. If the level was increased initially, it fell rapidly when cortisone was given, often becoming abnormally low. In those cases in which cessation of hormone treatment was followed by a "rebound" of clinical activity the plasma fibrinogen level often rose transiently, this rise being preceded by an increase in E.S.R. and re-appearance of C.R.P. In general, the plasma fibrinogen level returned to normal before C.R.P. disappeared and long before the E.S.R. fell to normal, and the authors suggest that such a fall is a reliable indicator of a recession of the inflammatory process rather than of its complete subsidence.

S. C. Milazzo.

Studies of Protein-Bound Carbohydrate in Rheumatic Disease. (Untersuchungen über das Verhalten eiweissgebundener Kohlenhydrate bei rheumatischen Erkrankungen.) GAMP, A. (1955). *Z. Rheumaforsch.*, **14**, 167. 5 figs, 38 refs.

At the Clinic for Rheumatic Diseases, Bad Kreuznach, Germany, 498 samples of serum from 302 patients with various forms of rheumatic disease were examined for the content of protein-bound carbohydrate. The results showed that the serum proteins of these patients contain fixed carbohydrates consisting mainly of galactose, mannose, and glucosamine. These components can be isolated from the proteins and quantitatively determined. This procedure revealed that glucosamine levels rise proportionately with the activity of the disease in most cases of acute rheumatoid arthritis and ankylosing spondylitis, but a similar rise was seen only rarely in cases of fibrositis, osteo-arthritis, and quiescent rheumatoid arthritis. Quantitative determination of the glucosamine level was found to be useful in evaluation of the activity in chronic inflammatory rheumatism, and also in the differential diagnosis between inflammatory and degenerative types of rheumatic diseases, being thought to be more useful in this respect than the erythrocyte sedimentation rate.

In discussion the author states that the increase in the serum content of protein-fixed carbohydrates is caused by a rise in the level of carbohydrate-rich globulins and a fall in that of albumins, as well as a rise in the carbohydrate content of some other serum protein fractions. An increase in the total serum proteins was not found to be a factor, nor is it thought that the increase is due to the appearance of abnormal carbohydrate–protein fractions.

G. W. Csonka.

Investigation of the Properties of a Substance with the Characteristics of a Tissue-specific Antibody occurring in the Serum in Cases of Polyarthritis and Rheumatic Endocarditis. (Untersuchungen über die Eigenschaften einer im Serum von Polyarthritikern und von Patienten mit rheumatischer Endocarditis vorkommenden Substanz mit den Merkmalen eines gewebsspezifischen Antikörpers.) STEFFEN, C., and SCHINDLER, H. (1955). *Schweiz. Z. allg. Path. Bakt.*, **18**, 287. 25 refs.

Working in the clinical laboratories of the Hanusch Hospital, Vienna, the first-named author, employing an anti-human-globulin (A.H.G.) deviation technique, has shown that the serum of patients suffering from rheumatoid arthritis and rheumatic endocarditis contains a substance with specific properties against cells of the heart, muscle, and joint capsules. Serum from healthy individuals and from patients suffering from diseases

such as tuberculosis and pneumonia did not contain this substance, while the latter had no effect on cells of the spleen or liver. It was concluded that the substance was of the nature of an incomplete antibody with a specific activity against fibro-muscular tissue. In the further studies here reported its properties were investigated by a deviation technique (using Coombs serum) and by elution. [For details of the procedures the origin should be consulted.]

Samples of serum from thirteen patients with cardiac disease incubated with cardiac tissue and mixed substrate; with eight of these, from patients with active rheumatic endocarditis, definite A.H.G.-deviation was obtained, but four tests against muscle substrate gave no deviation. In one case, which ultimately proved fatal, it was actually found possible to use ante-mortem serum against the patient's own tissues. In two cases it was shown that the level of circulating antibody decreased with clinical improvement. Of samples of serum from five patients with cardiac disease who acted as controls, four showed no deviation with muscle, heart, and mixed substrate, while the fifth revealed antibody activity against muscle and mixed substrate but not against heart substrate.

The sera of eight rheumatoid arthritic patients were next examined, those of five patients with neurasthenia and neuralgia being tested as controls. The former showed the presence of an antibody with specific action against muscle cells and mixed cells (from muscle, joint-capsules, and heart); four of these sera showed no specificity towards heart cells, but the remaining four revealed some specificity, and inquiry showed that three of these patients had old cardiac damage. The five control cases yielded negative results. Absorption and elution techniques gave comparable results.

David Preiskel.

Reaction of Streptococcal Agglutination relative to the RAS Factor in Rheumatoid Arthritis. Parts I and II. [In English.] THULIN, K. E. (1955). *Acta rheum. scand.*, **1**, 22. 7 figs, 25 refs.

The agglutination by sera from cases of rheumatoid arthritis of living Group-A streptococci pathogenic to man (L agglutination), of killed, autoclaved streptococci of the same origin (O agglutination), and of sensitized sheep erythrocytes was studied at the University of Lund, Sweden. All these tests are known to give positive results in varying degrees in cases of rheumatoid arthritis.

Electrophoretic separation of the different serum protein components was first undertaken, and the agglutination titre of the various components estimated. The L and O agglutinins were consistently found in the slower moving fractions of gamma globulin, while the R.A.S. factor (the unidentified "rheumatoid arthritis serum" factor responsible for the agglutination of sheep erythrocytes) was recovered from the faster moving gamma- and beta-globulin fractions. The titre of the R.A.S. factor was found to reach its maximum in those fractions in which those of the L and O agglutinins are decreasing or absent, showing that these agglutination factors are not identical.

Sera treated with carbon dioxide at 4° C. showed a significant reduction in titre of the L agglutinins and of the R.A.S. factor, without change in that of the O agglutinins. Titration of the precipitate formed with CO_2 demonstrated the presence in it of part of the R.A.S. factor but no L agglutinins. It is suggested that these experiments show that there is a relationship between L agglutinins and the R.A.S. factor whereas the O agglutination reaction appears to be entirely independent of the other two. Sera were then treated with 0·5 per cent. aluminium silicate (bentonite), which has been shown to precipitate only beta-globulins. This caused the complete disappearance of L agglutinins and the R.A.S. factor without having any effect upon the O agglutinin titre. However, the addition of electrophoretic fractions with a high titre of R.A.S. factor to the bentonite-treated serum resulted in reactivation of the L agglutinating factor without influencing the titre of the O agglutinins. As L agglutinins are associated mainly with the slow-moving gamma globulin and the R.A.S. factor with the fast-moving fraction this was not due to the introduction of fresh L agglutinins, but to a specific relationship between the R.A.S. factor and L agglutination.

Since human pathogenic streptococci contain polysaccharides closely related to certain substances present in mesenchymal tissues, namely, N-acetyl glucosamine and hyaluronic acid, the agglutinins which react with the streptococcal antigens in rheumatoid arthritis might be auto-antibodies developed against mesenchymal tissue products. In an attempt to test this hypothesis sera from cases of rheumatoid arthritis were treated for one hour at 52° C. with streptococcal C-substance, hyaluronic acid, N-acetyl glucosamine, and autoclaved synovial tissue and their agglutination titres then redetermined. L agglutination was found to be completely inhibited by synovial tissue, but not by the other polysaccharides. The effect on O agglutination was more variable, although all the substances tested generally reduced the titre and in some cases inhibited agglutination.

In view of these findings the author puts forward a new concept of the pathogenesis of rheumatoid arthritis, envisaging four phases:

(1) Hyaluronidase production is increased as a result of various disturbances, infectious, hormonal, and traumatic.
(2) Depolymerization of mesenchymal polysaccharides and hyaluronic acid occurs as a result of this increased enzymatic activity.
(3) Depolymerization products become bound to local or serum proteins and become antigenically active, with the production of auto-antibodies.
(4) An auto-allergic reaction results, producing inflammation and proliferation of synovial tissue and maintaining the continuous activity that is the normal course of rheumatoid arthritis.

[This is an important and significant addition to knowledge concerning the agglutination phenomena occurring in sera from cases of rheumatoid arthritis and their relationship, and to the development of the concept of rheumatoid arthritis as an auto-allergic reaction.]

Harry Coke.

Fibrinogen Polymerization Test in Active Rheumatic Disease. LOSNER, S., and VOLK, B. W. (1955). *Amer. J. med. Sci.*, **229**, 371. 1 fig., 24 refs.

After the administration of a therapeutic dose of heparin *in vivo* or the addition of a minute quantity to a blood sample *in vitro* the authors have observed that considerable amounts of fibrinogen remain in the serum separating after gross coagulation has taken place. They have therefore concluded that heparin interferes with the polymerization of fibrin, and in a study carried out at the Jewish Chronic Disease Hospital, Brooklyn, New York, have utilized this property in the investigation of the possible presence of polymerization-accelerators in the serum in various diseases. The method is described in detail. Blood is drawn one hour after the intravenous injection of 50 mg. heparin (or the heparin is added *in vitro*, 8 μg. to 3 ml. blood) and clotted at 37° C. in four tubes in aliquots of 3 ml. each, 0·3 ml. 0·1 M sodium citrate being added to the clotted blood at hourly intervals and the clot centrifuged down immediately. The supernatant serum is then investigated for the presence of fibrin, using the photoelectric prothrombin-time method, and the fibrinogen concentration is measured by determination of the density of the clot.

These tests were performed on the serum of twelve normal persons and of a number of patients with rheumatoid arthritis, rheumatic fever, and a variety of other clinical conditions, a total of 36 tests *in vivo* and 54 *in vitro* being carried out. A positive result was indicated by a complete consumption of fibrinogen. The results were negative in normal subjects, but were positive in active rheumatoid arthritis (22 cases) and active rheumatic fever (five cases). Moreover, these test results remained positive long after laboratory criteria of the activity of rheumatic fever had returned to normal and they were not affected by the administration of cortisone. In the tests on serum from patients with such other diseases as glomerulonephritis, lupus erythematosus, or carcinomatosis the results were negative. The mode of action of heparin is discussed. It is concluded that heparin, in addition to its anticoagulant properties, can delay the polymerization of fibrinogen, and that this action is accelerated in the serum of patients with active rheumatic disease. *E. G. L. Bywaters.*

Degenerative Lesions of Tendinous and Aponeurotic Tissues. (Les lésions dégénératives des tissus tendineux et aponévrotiques.) DELARUE, J., MIGNOT, J., PAYEN, J., and ROUSSEL, A. (1955). *Presse méd.*, **63**, 607. 9 figs, 12 refs.

In this paper from the Paris Faculty of Medicine attention is directed to changes in the state of the intercellular substance of tendinous and aponeurotic tissues in a variety of lesions, including synovial cysts ("ganglia"), tumours of tendon sheaths, lesions of knee-joint menisci, and Dupuytren's contracture. Of particular importance is the mucopolysaccharide material of the connective-tissue ground substance. The authors describe a histological study of tissue from 23 ganglia (mostly from the dorsum of the hand), sixteen examples of tendon rupture, and fifteen "histiocytic" tumours of tendon sheaths. Sections were stained with haemalum eosin, Masson's trichrome stain, and toluidine blue or methylene blue to show metachromasia, as well as with the last two dyes at varying *p*H to assess the apparent isoelectric point of tissue constituents. The periodic-acid–Schiff technique was also used.

In all the conditions above referred to the abnormal connective tissue present showed a positive periodic-acid–Schiff reaction, metachromatic staining, and intensified staining with toluidine blue and methylene at a *p*H of about 3·5. *H. A. Sissons.*

Persistently High Erythrocyte Sedimentation Rate. I. Diagnostic and Prognostic Aspects. II. With Good Prognosis. [In English.] LILJESTRAND, A., and OLHAGEN, B. (1955). *Acta med. scand.*, **151**, 425. 5 figs, 30 refs.

The case records of patients attending the out-patient medical clinic of Karolinska Sjukhuset, Stockholm, during the year 1941 were analysed with special reference to the incidence of unexplained elevation of the erythrocyte sedimentation rate (E.S.R.). In addition all cases in which there was a raised E.S.R. or hyperglobinaemia of uncertain origin seen during the period 1941–50 were reviewed.

The over-all frequency of such cases was low. Only about 0·3 per cent. of the out-patients seen during 1941 showed even a transitory unexplained rise in E.S.R. and in most cases this could be attributed to various infections. The very small number of cases of cancer presenting as a vague illness with a high E.S.R. is stressed. The authors consider that electrophoretic analysis of the serum proteins is of diagnostic value. Although malignant tumours do not produce any specific serum protein pattern, a rise in the α-globulin and fibrinogen values is suggestive. A raised γ-globulin value on the other hand is more suggestive of hepatic cirrhosis, collagen disease, or myeloma.

Among 790 out-patients (out of a total of 9,140 seen in 1941) in whom the E.S.R. was shown to be raised, only 32 had insufficient signs and symptoms to make a diagnosis possible at the first attendance. Of these, nine were subsequently found to have a permanently raised E.S.R. which, over a period of observation of 9 to 13 years, was unassociated with any manifestation of disease. This figure of nine was brought to a total of 37 after analysis of in-patient and out-patient records for the period 1941–50. In all but two of these cases following fourteen of the 35 cases the raised E.S.R. could be definitely or probably attributed to disease. In the remaining 21 the benign nature of the elevated E.S.R. was supported by the results of clinical and laboratory investigations carried out over periods ranging from 3 to 20 years. All but one of these patients were females. Electrophoretic studies of the plasma protein patterns showed that four main types of plasma protein disturbance were distinguishable:

(1) Serum hypergammaglobulinaemia (nine cases);
(2) Increased plasma β-globulin and fibrinogen values (five cases);

(3) Increased plasma fibrinogen value (five cases); and
(4) the presence of abnormal protein components (two cases). *A. Brown.*

Complementary Activity of Whole Serum and of its Separate Fractions in Ankylosing Spondylitis and Rheumatoid Arthritis. (L'attività complementare del siero in toto e delle singole frazioni nella spondilite anchilosante e nell'artrite reumatoide.) LUCA, S., TUZI, T., and VOLPICELLI, M. (1955). *Progr. med. (Napoli)*, **11**, 520. 13 refs.

Serum Lipids in Rheumatoid Arthritis. (Über die Serumlipoide bei der primär chronischen Polyarthritis.) ENZINGER, J. (1955). *Wien. Z. inn. Med.*, **36**, 357. 2 figs, 13 refs.

Blood Cell Phagocytosis in Cases of Connective Tissue Disorders and Histological Changes after Local Injection of Patient Serum into Animals. [In English.] WASASTJERNA, C., and WEGELIUS, O. (1955). *Acta med. scand.*, **152**, 175. 8 figs, 8 refs.

Significance of Lysozyme in Acute Articular Rheumatism. (Über die Bedeutung des Lysozyms für den akuten Gelenkrheumatismus.) CASELLI, P., and SCHUMACHER, H. (1955). *Z. Rheumaforsch.*, **14**, 308. 3 figs, 12 refs.

Role of the Haemolytic Streptococcus in the Aetiology of Acute Articular Rheumatism. (Rôle du streptocoque hémolytique dans l'étiologie du rhumatisme articulaire aigu.) COSTE, F. (1955). *Rev. argent. Reum.*, **20**, 122.

Reaction to Diphenylamine in Rheumatology. (La reazione alla difenilamina in reumatologia.) RIVANO, R., SOLARI, S., and CAPPONI, G. (1955). *Reumatismo*, **7**, 294. 2 figs, 8 refs.

Comparative Study of the Agglutination Reaction with Sensitized Sheep Erythrocytes and the Antistreptolysin Reaction. (Vergleichende Untersuchungen über die Agglutinationsreaktion sensibilisierter Hammelblutkörperchen und die Anti-Streptolysin-Reaktion.) FRANK, A., and SCHIMANSKI, J. (1955). *Z. Rheumaforsch.*, **14**, 238. 24 refs.

Diphenylamine Reaction in Rheumatic Diseases. (Die Diphenylamin-Reaktion bei rheumatischen Erkrankungen.) ROTHER, K. (1955). *Z. Rheumaforsch.*, **14**, 215. 1 fig., 3 refs.

Synovial Fluid in Rheumatoid Arthritis. (Das Gelenkspunktat bei der primär chronischen Polyarthritis.) HUNZIKER, H. (1955). *Z. Rheumaforsch.*, **14**, 217. 5 refs.

Electrophoretic Pattern of the Proteins of the Synovial Fluid and the Serum before and after Treatment with Hydrocortisone and Phenylbutazone. (Il quadro elettroforetico delle proteine del liquido sinoviale in rapporto al quadro serico e sue variazioni dopo trattamento con hydrocortone e butazolidina.) ROBECCHI, A., DANEO, V., and RICCARDINO, N. (1955). *Reumatismo*, **7**, 209. 5 refs.

Electrophoretic Studies of the Serum Proteins in Acute Rheumatism. (Rilievi elettroforetici sulla disproteidemia dell'infezione reumatica acuta.) ANTONACI, B. L. (1955). *Reumatismo*, **7**, 229. 4 figs, bibl.

Formalin Arthritis in Rats treated with Pyrazolidin and Amidopyrine. (Contributo allo studio dell'artrite da formalina in ratti trattati con pirazolidina-piramidone.) GAGLIO, M., and MAZZONE, O. (1955). *Reumatismo*, **7**, 255. Bibl.

Serological Tests in the Diagnosis of Rheumatoid Arthritis. (Las pruebas serológicas en el diagnóstico de la poliartritis crónica primaria.) FOZ, A., BATALLA, E., and BARCELÓ, P. (1955). *Rev. esp. Reum.*, **6**, 66.

Potassium and Sodium Contents of the Serum in Rheumatoid Arthritis. [In English.] LALLIOMÄKI, L., and KASANEN, A. (1955). *Ann. Med. intern. Fenn.*, **44**. 141. 2 figs, 3 refs.

ACTH, Cortisone, and Other Steroids

Corticotropin (ACTH) in Heart Disease: its Paradoxical Effect on Sodium Excretion in Resistant Congestive Failure. CAMARA, A. A., and SCHEMM, F. R. (1955). *Circulation (N.Y.)*, **11**, 702. 3 figs, 12 refs.

In this interesting article from the Deaconess Hospital, Great Falls, Montana, the authors report the apparently paradoxical action of ACTH (corticotrophin) in 21 cases of chronic congestive heart failure with persistent oedema. The cases comprised eight of arteriosclerotic heart disease, three of hypertensive heart disease, eight of rheumatic heart disease, and two of cor pulmonale. Despite the usual diuretic regimen, which included the administration of ammonium chloride and mercurial diuretics and other relevant treatment, these patients were not losing their oedema.

While this diuretic regimen was continued ACTH was given in doses of 10 to 25 mg. 6-hrly for 10 to 12 days. The results were remarkable in that some patients lost as much as 17·5 kg. body weight in 13 days. Three types of response were noted:

(1) A spontaneous diuresis after 4 to 6 days;
(2) A profuse diuresis after the ACTH had been stopped; and
(3) A greatly improved response (in ten of the cases) to mercurial diuretics during or after the administration of ACTH.

The treatment failed in four patients of which three were cases of rheumatic heart disease. In some cases there was an initial slight increase in the oedema.

In conclusion the authors speculate on the possible mode of action of ACTH in these circumstances and suggest that it may inhibit the release of a DOCA-like, sodium-retaining hormone from the adrenal cortex, or alternatively, that it may have some direct action on the failing myocardium. *G. S. Crockett.*

Treatment of the Nephrotic Syndrome with Corticotropin (ACTH) and Cortisone. A Four-and-one-half-year Survey of Results with Short-term Courses. HEYMANN, W., SPECTOR, S., MATTHEWS, L. W., and SHAPIRO, D. J. (1955). *Amer. J. Dis. Child.*, **90**, 22. 13 refs.

The results obtained with short-term courses of corticotrophin (ACTH) or cortisone in 64 children aged 1 to 9 years with the nephrotic syndrome are reported. No significant difference between the effects of the two drugs was noted. An over-all incidence of diuresis of approximately 80 per cent. in 153 courses of ACTH or cortisone was obtained, diuresis occurring rather more frequently during administration of the drug than after withdrawal. The incidence of diuresis was lower in children in whom the disease later progressed to renal failure, even although there was no indication at the time of progressive renal disease. No attempt was made to distinguish cases of pure nephrosis from those of nephrotic nephritis, but patients with fixed azotemia or persistent hypertension were excluded.

Of the 64 children, 43 required only three courses of treatment, the total stay in hospital of these being 1 to 1½ months. However, although morbidity was much reduced by administration of these drugs, the mortality rate was not significantly improved; seventeen patients died, fourteen of them in renal failure.

Margaret D. Baber.

Treatment of Peri-Arthritis of the Shoulder with Hydrocortisone. CRISP, E. J., and KENDALL, P. H. (1955). *Brit. med. J.*, **1**, 1500. 2 figs, 10 refs.

The pathological changes associated with peri-arthritis of the shoulder are discussed and it is pointed out that theoretically such a condition should respond to cortisone or hydrocortisone. However, the previously reported results of hormonal treatment have varied widely.

The present authors, working at Guy's Hospital, London, have improved their own results by changing their technique of injection slightly. They now introduce hydrocortisone at three different points: anteriorly into the subacromial bursa, antero-laterally into the long head of the biceps, and posteriorly into the joint capsule, injecting 50 mg. hydrocortisone in a 2-ml. suspension with the addition of 1,000 units hyaluronidase and 2 to 3 ml. 2 per cent. procaine.

Of fifty acute cases treated by this method, 36 (72 per cent.) progressed to complete recovery in 7 to 14 days and eleven (22 per cent.) were improved.

Of 23 chronic cases of the "frozen-shoulder" type, thirteen (56 per cent.) regained full function in 4 to 6 weeks after injections of hydrocortisone and shoulder exercises, and five (22 per cent.) were improved.

Oswald Savage.

Local Hydrocortisone in de Quervain's Disease. CHRISTIE, B. G. B. (1955). *Brit. med. J.*, **1**, 1501. 7 refs.

The author points out that since 1895, when de Quervain first described the stenosing tenosynovitis at the radial styloid process with which his name is associated, of the many methods of treatment which have been suggested, operation alone has hitherto achieved success. Various types of injection tried in the past have given poor results, but in view of the reported success of local injections of hydrocortisone in the treatment of "tennis elbow" and other soft-tissue lesions it was decided to undertake a controlled trial of this method in twenty consecutive cases of de Quervain's disease seen at the Middlesex Hospital, London.

The patients were divided into two groups. Group A received 25 mg. hydrocortisone injected into the tendon sheath after infiltration with 1 ml. 2 per cent. procaine solution, and Group B received an injection of procaine alone.

Of the ten patients in Group A, seven experienced complete relief of symptoms for 100 days or more, whereas no patient in Group B experienced relief for more than 2 days. When patients in the latter group were later treated with hydrocortisone, nine of the ten lost their pain for a substantial period. *Oswald Savage.*

Hydrocortisone Tertiary-butylacetate by Intra-Articular Injection. HOLLANDER, J. L., BROWN, E. M., JESSAR, R. A., UDELL, L., SMUKLER, N. M., BOWIE, M. A. (1955). *J. Amer. med. Ass.*, **158**, 476. 18 refs.

In a search for a preparation capable of prolonging the local palliative effect of the intra-articular injection of hydrocortisone in inflammatory arthritic conditions the authors tried the effect of a micro-crystalline suspension of a less soluble ester of hydrocortisone, namely, hydrocortisone tertiary-butylacetate. At the University of Pennsylvania Hospital, Philadelphia, 92 patients with rheumatoid arthritis and 79 with osteo-arthritis of one or both knees (who had previously been treated with intra-articular injections of hydrocortisone acetate) were given, without their knowledge, the new ester instead in identical dosage.

A comparison of the results in the two periods of treatment showed that the new ester produced an amelioration which was greater and of longer duration in about 60 per cent. of the total of 171 cases; in about 5 per cent. hydrocortisone acetate was considered more effective, and in the remaining 35 per cent. there was no appreciable difference between the effect of the two hormone preparations. The most significant differences were noted in the patients with osteo-arthritis. There was an exacerbation of the joint symptoms in three patients after the injection of hydrocortisone tertiary-butylacetate and in four after hydrocortisone acetate, but no other complications were encountered.

K. C. Robinson.

Intravenous Hydrocortisone. NABARRO, J. D. N. (1955). *Arch. Middx Hosp.*, **5**, 79. 5 figs, 11 refs.

It is first pointed out that in the treatment of acute adrenal insufficiency, when it is necessary rapidly to raise the level of circulating hormone, intravenous

administration of hydrocortisone is much more effective than intramuscular. Though it has no advantage over oral administration of cortisone, which is followed within an hour by a significant rise in the plasma level of 17-hydroxycorticosteroids, it may be of great value in the patient who is unconscious or vomiting. The author describes the results of intravenous infusion of hydrocortisone in two cases of Addisonian crisis, one case of acute adrenal insufficiency during adrenalectomy, one of adrenal insufficiency after operation following prolonged cortisone therapy, in one of severe post-operative shock, and in one of Cushing's syndrome as a diagnostic test to distinguish between adrenal tumour and hyperplasia.

In the two cases of Addisonian crisis the results were disappointing, and this is attributed partly to the fact that the solution was made up in 5 per cent. glucose and not normal saline and partly to the fact that no additional cortisone was given by mouth or intramuscular injection. Hydrocortisone for intravenous use is supplied in ampoules containing 100 mg. in 20 ml. 50 per cent. alcohol, this being added to 0·5 or 1·0 litre of an isotonic fluid. Usually the Addisonian crisis is associated with sodium depletion and the diluent should therefore be normal saline. Since the effect of intravenous hydrocortisone is transient, the level of circulating hormone falling rapidly at the end of the infusion, it is necessary to give cortisone intramuscularly as well and to continue the infusions until this becomes effective or oral administration is possible. The author suggests the following regimen for the treatment of patients in Addisonian crisis. If the patient can take cortisone by mouth 100 mg. should be given every 4 hours until improvement is obvious; in other cases 100 mg. cortisone should be given intramuscularly and an infusion of hydrocortisone in normal saline begun. For the first 2 hours the rate of infusion should be 25 mg. an hour; subsequently it should be 12·5 mg. an hour. The infusion should be continued for at least 8 hours, and as soon as possible cortisone should be given by mouth. In cases in which the plasma potassium level is very high an intramuscular injection of 5 to 10 mg. deoxycortone is advisable.

Acute adrenal insufficiency in which there is no sodium depletion may occur during operation or when a patient with adrenal atrophy is subjected to severe stress. Two such cases are described, in both of which there was a satisfactory response to intravenous infusion of hydrocortisone in 5 per cent. glucose.

Rukes and others (*Metabolism*, 1954, **3**, 481) reported cases of severe surgical shock uninfluenced by blood or plasma transfusion or by noradrenaline which responded to intravenous infusion of hydrocortisone. In one case of this type in the present series benefit was only temporary. The author suggests that the use of hydrocortisone in such cases merits further investigation. *Kenneth Stone.*

Corticotrophin Intravenous Infusion Therapy in Rheumatic Conditions. BEATTIE, J. W., and HARTFALL, S. J. (1955). *Brit. med. J.*, **1**, 149. 3 figs, 48 refs.

This paper from the University of Leeds records the authors' experience with corticotrophin (ACTH) administered by slow intravenous infusion in the treatment of rheumatic conditions. Between August, 1951, and October, 1953, 425 patients, of whom 329 suffered from rheumatoid arthritis of all grades of severity, were treated in this way, other accepted methods of treatment being employed as necessary at the same time. Variations ranging from 5 mg. to 25 mg. were made in the dose of ACTH given in each infusion until it was clear that 20 or 25 mg. gave the maximum effect. After preliminary trials of various vehicles the majority of patients received hormone in one litre of normal saline, and it was found that the optimum duration for each infusion was 18 to 24 hours. Generally the practice was to administer three infusions at intervals of 4 to 7 days during each admission to hospital, lasting usually from 2 to 4 weeks. In a total of 1,490 infusions no serious complication arose, the most frequent being the development of local venous thrombosis, which made subsequent treatment difficult.

Among those patients who benefited by the treatment, the majority experienced a striking improvement after the first infusion which was maintained, but not increased, by subsequent infusions. Euphoria was induced in most cases and the authors regard this as a valuable contribution to the rehabilitation programme in patients who are depressed and apathetic. A sense of increased physical well-being, improvement in appetite, and the dissipation of malaise were also marked. Altogether, some degree of improvement was obtained in 89 per cent. of cases of rheumatoid arthritis, the greatest change being in the functional capacity. Analysis of the results showed that the most improvement occurred where the disease had been present for less than one year. On the other hand the degree of improvement obtained was much the same in all age groups. *Oswald Savage.*

Eosinophil Response to Graded Doses of ACTH and Cortisone in Man. MILLER, A. T. (1955). *J. appl. Physiol.*, **7**, 663. 7 refs.

Studies at the University of North Carolina have shown the eosinophil count to be superior to other commonly used indices of adrenocortical response to single injections of ACTH. The present study was designed to provide the basis for a more detailed analysis of the factors influencing the eosinophil response to both ACTH and cortisone. To twenty healthy male dental students ACTH was given intramuscularly in doses of 5, 10 and 20 *U.S.P.* units, and cortisone acetate was given orally in doses of 12·5, 25, and 50 mg. In every case the drug or a control saline injection was given at noon, and eosinophil counts were made at 8 a.m., noon, and 4 p.m. There was an interval of at least one week between successive tests, each subject being tested twice at each dose level of ACTH and cortisone.

The threshold dose for intramuscular ACTH was found to be less than 5 units and for oral cortisone less than 12·5 mg. For ACTH, in the dose range 0 to 10 units, the eosinophil response was found to distinguish between doses differing by 5 units, and in the dose range

10 to 40 units to distinguish doses differing by 10 units. The author points out that the minimum difference in dose detectable in this way increases with increasing dose because of the asymtotic approach to complete depression of the circulating eosinophil count. The minimum difference in dose that could be detected in the case of cortisone was of the order of 12·5 mg. over the whole range of 0 to 50 mg., the dose–response relationship being almost perfectly linear over this range.

In discussion the author suggests that from these findings it would appear that the eosinophil response to hormonal stimulus is not merely superimposed upon a diurnal trend, but that the diurnal trend is actually abolished by the administration of hormone. Thus, strict standardization of tests to correct for directional changes in the eosinophil count during the period before testing does not appear to be necessary.

Adrian V. Adams.

Effect of Corticotrophin and Cortisone on Neutral 17-Ketosteroid Metabolism as demonstrated by Microchromatographic Fractionation of Urinary Extracts from Twelve Treated Patients. [In English.] POND, M. H. (1955). *Acta endocr.* (*Kbh.*), **19**, 1. 17 refs.

The effect of corticotrophin and of cortisone on the excretion of 17-ketosteroids was studied at King's College Hospital Medical School, London, in twelve patients with normal or hypo-adrenal function. Corticotrophin produced a rise in the excretion of the 11-oxy-17-ketosteroid and β-fractions in patients with low adrenal activity, but gave variable results in patients with normal adrenal function. After administration of cortisone there was general depression of the total 17-ketosteroid excretion with a rise in excretion of the 11-oxy-17-ketosteroid fraction. *F. W. Chattaway.*

Comparison of Some Commonly-Used Indices of Adrenal Cortical Function. MILLER, A. T. (1955). *J. appl. Physiol.*, **7**, 660. 15 refs.

The study here described from the University of North Carolina Medical School, Chapel Hill, N.C., was carried out on nine healthy male students and was designed to compare the value of haematological and urinary changes as indices of the response of the adrenal cortex to the injection of small, graded doses of ACTH (corticotrophin). The ACTH was given at noon in doses of 5, 10, 20, and 40 *U.S.P.* units by intramuscular injection, and blood samples for determination of the leucocyte count were taken at 8 a.m., noon, and 4 p.m., and urine collected over three 4-hr periods, 8 a.m. to noon, noon to 4 p.m., and 4 p.m. to 8 p.m., for analysis of sodium, potassium, uric acid, and 17-ketosteroid content. No attempt was made to control the diet or activities of the subjects, but no subject with recent exposure to stress (for example, a dental extraction or immunization procedure) was included in the study and an interval of at least one week was allowed between two consecutive tests on the same individual.

The changes in the leucocyte count were related approximately, but not linearly, to the dose of ACTH given, that in the number of eosinophil granulocytes being the most closely correlated. The 4-hr eosinophil response is therefore recommended as the most suitable for determining quantitatively the response to small doses of ACTH or single acute stresses. The variability of the response as determined by changes in the sodium, potassium, and 17-ketosteroid excretion in the urine and the uric acid : creatinine ratio is discussed. It is concluded that these urinary indices lack the specificity necessary for determining quantitatively the adrenocortical response to small, graded doses of ACTH.

Adrian V. Adams.

Effect of 9-α-Fluoro Hydrocortisone on Adrenal Hyperfunction in Cushing's Syndrome. COPE, C. L., and HARRISON, R. J. (1955). *Brit. med. J.*, **2**, 457. 3 figs, 11 refs.

9-α-fluoro hydrocortisone has been reported to have twenty times the therapeutic potency of cortisone and about one-tenth of the sodium-retaining power of aldosterone, and has been shown to have an inhibitory effect on the normal adrenal cortex. Because the breakdown products of cortisone and hydrocortisone are essentially like those occurring naturally in the urine and plasma, it is impossible to assess the inhibitory effect of cortisone on the normal or hyperplastic adrenal cortex by determination of the excreted adrenal steroids; this, however, does not hold for 9-α-fluoro hydrocortisone, the breakdown products of which are different from those derived from hydrocortisone. Taking advantage of this fact the authors have observed the inhibitory effect of 9-α-fluoro hydrocortisone in a typical case of Cushing's syndrome, in which the diagnosis was later confirmed by laparotomy. Adrenal function was assessed by the measurement of the daily excretion of 17-ketosteroids, 17-ketogenic steroids, and hydrocortisone. They found that on administration by mouth of a daily dose of 5 mg. 9-α-fluoro hydrocortisone (equivalent to about 100 mg. cortisone) hydrocortisone excretion was reduced by 50 per cent., and with a dose of 15 mg. daily by 80 per cent. The output of hydrocortisone returned to its previous high level when the drug was withdrawn. The excretion of 17-ketosteroids and ketogenic steroids was uninfluenced.

From all available evidence it appeared likely that the new steroid had suppressed the production of hydrocortisone by the adrenal cortex. It is considered that this action is probably analogous to that of cortisone in the adrenogenital syndrome, in which cortisone suppresses excessive ketosteroid excretion if this is due to hyperplasia, but not if it is due to tumour formation. By the use of 9-α-fluoro hydrocortisone it might, therefore, be possible to differentiate between Cushing's disease due to cortical hyperplasia—as was probably the case in the patient studied—and that due to tumour.

The authors conclude that the inhibitory effect of this steroid is mediated through the pituitary gland by a sudden increase in the plasma concentration of hydrocortisone-like substances. *J. N. Harris-Jones.*

Metabolic Effects of Metacortandracin [Prednisone] and 9-α-Fluoro Hydrocortisone Acetate. (Effetti metabolici del metacortandracin e del 9-α-fluoroidrocortisone acetato.) SALA, G., D'AMICO, G., PASARGIKLIAN, E., AMIRA, A., and BALLABIO, C. B. (1955). *Reumatismo*, 7, 127. 10 figs, 24 refs.

9-α-fluoro hydrocortisone causes an increase of the body fluids (intra- and extracellular) with retention of water, chlorides, and sodium and increased potassium excretion (Na : K being increased). [Incomplete] studies of the carbohydrate metabolism seem to show a diminished sensitivity to insulin. The blood eosinophil count shows no definite change. The excretion of urinary 17-ketosteroids is much diminished. The adrenal function is depressed, even after only short treatment.

Prednisone produces an increase in the urinary sodium excretion and diuresis without obvious alteration of the plasma electrolytes. The effect on carbohydrate metabolism is not convincing, but perhaps slightly diabetogenic. The eosinophil count is diminished, the urinary 17-ketosteroid excretion decreased. There is little influence on the excretion of uric acid in gouty subjects, although clinically the result was equal to that of phenylbutazone and was excellent in one case. Adrenal function is depressed.

There does not seem to be any causal relation in the case of either steroid between its influence on the mineral and carbohydrate metabolism and its effect on the signs of inflammation and its antiphlogistic action.

V. C. Medvei.

Metabolic, Functional, and Clinical Aspects of Treatment with "Deltacortene" [Prednisone]. (Alcuni aspetti metabolici, funzionali e clinici registrati in corso di terapia con deltacortene.) BONATI, B., BERGAMINI, A., RANCATI, G. B., and TEDESCHI, G. F. (1955). *Minerva med. (Torino)*, **2**, 26. 5 figs, 24 refs.

At the Institute of Clinical Medicine and Therapeutics of the University of Modena, eight patients with a variety of conditions were treated with prednisone ("Deltacortene") and its effects carefully evaluated. The cases included one of adrenal virilism, two of rheumatoid arthritis, one of ankylosing spondylitis, three of bronchial asthma, and one of lupus erythematodes with arthritis. The drug was given by mouth in three or four doses daily, the total dosage on the first day being 35 mg., followed by 30 mg. for 3 days, 20 mg. for 3 days, 15 mg. for 4 days, and 10 mg. thereafter. The period of treatment ranged from 10 to 35 days. A dosage of less than 10 mg. daily did not appear to be effective.

Clinically, the results of treatment were satisfactory in all cases and much superior to those obtained with cortisone—for example, the patient with adrenal virilism started menstruating after 12 days compared with 45 days with cortisone in doses three times greater. One of the patients with asthma, who had an active duodenal ulcer in addition, was able to continue treatment with prednisone, whereas the administration of ACTH or cortisone had caused severe epigastric pain and had had to be discontinued. The drug's marked diuretic effect was confirmed; it was noticeable in the first 4 to 6 days of treatment and was accompanied by increased urinary excretion of chlorides. No other side-effects were observed.

Laboratory investigation of the endocrine effects showed that after 7 days there was a considerable reduction in the urinary excretion of 17-ketosteroid and a modest increase in that of 11-oxycorticoids; the urinary excretion of gonadotrophins was unchanged. Studies of renal function indicated that there was an increase in glomerular filtration and a decrease in tubular reabsorption of water. Blood coagulation was not affected. After 15 days' treatment the serum globulin content had become normal in one patient with rheumatoid arthritis, and an increase in the serum cholesterol level was noted in six other patients.

The effects of prednisone on the urinary steroid and gonadotrophin excretion suggest that it acts in part by a suppressive effect on the anterior lobe of the pituitary gland.

V. C. Medvei.

Meticorten and 9-α-Fluoro Hydrocortisone in the Treatment of Allergic Disorders. ARBESMAN, C. E., and EHRENREICH, R. J. (1955). *J. Allergy*, **26**, 189. 7 refs.

In the treatment at Buffalo (New York) General Hospital of eight patients with severe bronchial asthma which had been satisfactorily controlled by cortisone or hydrocortisone in doses of 30 to 70 mg. per day, these drugs were replaced experimentally by 9-α-fluoro hydrocortisone, which was given orally in a dose of 2 to 4 mg. daily (in one case 8 mg.). All the patients got rapidly worse [as would be expected with such a minute dose, which would be more suitable as a placebo] and it was concluded that the substance is of no value in allergic disorders.

The effect of the new synthetic corticosteroid "Meticorten" (Metacortandracin, prednisone) was then studied in twenty asthmatic patients most of whom had been maintained for some time with cortisone, hydrocortisone or ACTH, a dose of 5 mg. Meticorten being substituted for each 20 mg. hydrocortisone or each 25 mg. cortisone. Of the sixteen cases in which the treatment was so changed, in fifteen the condition was well controlled by the new drug, of which the average maintenance dose required was only 10·2 mg. per day compared with 53·1 mg. cortisone and 41·6 mg. hydrocortisone. Treatment had to be interrupted in one case because of severe epigastric pain which, however, disappeared when Meticorten was discontinued. One patient who had not previously received cortisone was well maintained on 10 to 15 mg. Meticorten per day; however, two other patients, one with perennial rhinitis and one with giant urticaria, derived no benefit. In six cases in which cortisone or hydrocortisone had caused water retention this disappeared when Meticorten was substituted. No increase of blood pressure was observed in any of the patients treated with Meticorten. It is concluded that Meticorten is, weight for weight, three to four times as effective as hydrocortisone, and four to five times as effective as cortisone.

H. Herxheimer.

Clinical Trial of Metacortandracin. (Esperienze cliniche con il metacortandracin.) GALLI, T., and SOLARI, S. (1955). *Minerva med.* (*Torino*), **2**, 14. 6 refs.

At the Medical Clinic of the University of Genoa Metacortandracin (prednisone) was tried in the treatment of 21 patients, twelve of whom were suffering from rheumatoid arthritis, one from gouty polyarthritis in a subacute phase, one from early scleroderma, six from osteo-arthritis with acute pain, and one from the "shoulder–hand" syndrome following myocardial infarction, with swelling of the hand and sub-ankylosis of the shoulder. In the six cases of osteo-arthritis the patients' age and sex are not given; of the remainder, seven were men and eight women, their ages ranging between 17 and 75 (but mainly between 30 and 60). Only the short-term results (up to 30 days) are reported and the effect of interruption of the treatment was not studied.

Metacortandracin was found to have an anti-rheumatic effect four to six times greater than that of cortisone and to be more effective than hydrocortisone. It did not show any influence on water and salt metabolism except for a very slight diminution in the serum potassium level. In two cases there was an initial increase of the blood pressure, which returned to normal when the dosage was reduced. The dosage (in rheumatoid arthritis) was as follows: 20 mg. daily (in four doses) for the first 3 days; 15 mg. for the next 3 days; 10 mg. for 10 days; 7·5 mg. for 4 days; and 5 mg. daily thereafter as a maintenance dose. In no case was epigastric pain, acne, erythema, or psychological disturbance observed. A very slight degree of moon-face developed in two cases, and excessive perspiration in one.

The introduction of Metacortandracin is, in the opinion of the authors, a real step forward in the steroid treatment of rheumatic disorders. *V. C. Medvei.*

Role of Gastric Secretions in Activation of Peptic Ulcers by Corticotropin (ACTH). HIRSCHOWITZ, B. I., STREETEN, D. H. P., POLLARD, H. M., and BOLDT, H. A. (1955). *J. Amer. med. Ass.*, **158**, 27. 4 figs, 15 refs.

The authors have investigated the effect of ACTH on gastric secretion in five healthy medical students with no radiological evidence of peptic ulcer who were given 25 units ACTH (corticotrophin) every 12 hours for 6 days. This produced an adequate adrenal response in all the subjects, as shown by a rise in the 17-hydroxycorticoid excretion and a fall in the circulating eosinophil count.

Analysis of the aspirated gastric juice showed a marked fall in viscosity, a slight fall in the volume of total gastric secretion, a moderate increase in concentration of pepsin, and a slight increase in concentration of acid; the absolute amounts secreted showed little change. The blood pepsin level also showed little change, but the urinary pepsinogen excretion increased greatly. It is pointed out that this must have been due to renal and not to gastric factors and that in the circumstances of the experiment, and even under basal conditions, urinary pepsinogen excretion is a very unreliable guide to gastric pepsin secretion.

Of particular interest are the authors' observations on a sixth medical student on whom several previous gastric tests had been carried out for research purposes with no untoward results. On the present occasion after 90 hours of ACTH administration he developed epigastric pain, vomiting, and gastric distension. Radiography revealed the presence of a post-bulbar duodenal ulcer—which had disappeared on re-examination 26 days later. There had been no observed rise in acid or pepsin secretion before the development of symptoms, although these values did increase later, suggesting that increased gastric secretion is not a cause but a consequence of exacerbation of duodenal ulcer. On the other hand the content of visible mucus and the viscosity of the gastric juice fell to a greater extent in this subject under the influence of ACTH than they did in any of the other five subjects. The authors suggest that changes in the properties or in the rate of production of gastric mucus may be of importance both in the exacerbation and healing of peptic ulcer. *T. D. Kellock.*

Studies on the Antipyretic Action of Cortisone in Pyrogen-Induced Fever. ATKINS, E., ALLISON, F., SMITH, M. R., and WOOD, W. B. (1955). *J. exp. Med.*, **101**, 353. 6 figs, bibl.

In this study of the antipyretic action of cortisone, carried out at Washington University School of Medicine, St. Louis, fever was induced in male rabbits weighing 2·5 to 3·5 kg. by means of "Pyromen", a highly purified polysaccharide from a species of *Pseudomonas*, or by native dextran with an average molecular weight of between 200,000 and 300,000, or by injecting typhoid vaccine. One group of animals received 25 mg. cortisone twice daily for the 3 days preceding the experiment, another group remaining untreated as a control. On the day of the experiment the treated group received a further injection of 25 mg. cortisone, and both groups were then given Pyromen. In both groups there was a transient fall in the leucocyte count, but only the control group showed a significant rise in temperature. In a repetition of the experiment using dextran as the pyogen, a similar result was obtained.

Two experiments were then carried out to test whether the serum factor (known to be involved in the action of pyrogens) was affected by cortisone:

In the first, typhoid vaccine incubated with serum from cortisone-treated rabbits was injected into rabbits made tolerant to this pyrogen. The latent period of the response was identical with that in tolerant rabbits given typhoid vaccine incubated with normal serum, thus showing that pretreatment of an animal with cortisone did not eliminate the serum factor.

In the second experiment the injection of typhoid vaccine incubated with normal serum did not produce fever if the rabbits had previously been treated with cortisone.

The authors conclude that the antipyretic effect of cortisone does not involve the leucopenic reaction nor the fever-accelerating factor present in the serum.

P. A. Nasmyth.

Prednisone ("Meticorten") and Prednisolone ("Meticortelone") in Ophthalmology. KING, J. H., and WEIMER, J. R. (1955). *Arch. Ophthal.* (*Chicago*), **54**, 46. 3 figs, 5 tables, 9 refs.

Recently two potent and atoxic corticosteroids have been synthesized: prednisone and prednisolone. They are two to four times as active as cortisone and hydrocortisone; on the other hand they induce less potassium excretion and very little sodium retention in therapeutic dosage. The authors confirmed their anti-inflammatory properties in fifteen rabbits with uveitis induced by horse-serum. 54 patients with various ocular inflammations were treated with the new steroids and several showed dramatic responses even where other steroids were ineffective. They were found to be more potent in ophthalmological conditions than were cortisone or hydrocortisone. *S. J. H. Miller.*

Scleromalacia Perforans treated with Cortisone. A Clinical Report with Some Remarks about Ulcerative Scleritis. GJESSING, H. G. A. (1955). *Acta ophthal.* (*Kbh.*), **33**, 229. 3 figs.

The literature of this rare disease is reviewed. The lesions are typically a symmetrical thinning of the temporal side of the sclera of each eye, with a well-marked margin. Uncommonly it may perforate, more usually the uvea may bulge the conjunctiva which covers it. There is a marked association with polyarticular rheumatism. The author suggests there may be an analogy between the condition and osteomalacia of pregnancy and that calcium, phosphorus and vitamin D should be added to the diet. *Lorimer Fison.*

Syndrome following Abrupt Cessation of Prolonged Cortisone Therapy. HENNEMAN, P. H., WANG, D. M. K., IRWIN, J. W., and BURRAGE, W. S. (1955). *J. Amer. med. Ass.*, **158**, 384. 14 refs.

The characteristic clinical picture which is observed following abrupt withdrawal of cortisone after prolonged administration is described. At the Massachusetts General Hospital nineteen patients with chronic asthma received cortisone for periods varying from 11 to 38 months (average daily dose 40 to 100 mg.). Between 24 and 48 hours after the last dose headache, nausea, vomiting, and restlessness developed, with generalized malaise and, in several instances, tender muscles and marked arthralgia. Symptoms became more severe for several days and then rather promptly lessened, disappearing entirely without treatment after 2 to 5 days. In general, the longer the duration of cortisone administration, the more severe were the symptoms on cessation of treatment.

The alarming clinical state of these patients was not associated with any significant changes in vital signs or in the responses to laboratory tests. The cause of the withdrawal syndrome is not at the present clear. When six of the patients were given an intravenous infusion of 500 ml. 0·9 per cent. saline solution daily for 1 to 3 days their symptoms were somewhat ameliorated, suggesting that adrenal insufficiency might be a cause. Asthma returned in a severe form necessitating resumption of cortisone therapy after an average of 8 days in those patients who did not receive saline infusions and after an average of 26 days in those given saline. Thus in all cases asthma returned only after the withdrawal symptoms had spontaneously cleared.

[This withdrawal syndrome is also observed in some patients given cortisone for rheumatoid arthritis, so it is not necessarily confined to allergic patients.]

G. B. West.

Mineral and Protein Metabolism and Adrenocortical Function in Senile Osteopathies. (Le métabolisme minéral-protidémique et la fonction cortico-surrénale dans les ostéopathies séniles.) MORPURGO, M., MARS, G., BONESSA, C., and BOSELLI, A. (1955). *Presse méd.*, **63**, 312. 11 refs.

The study here reported from the Institute of Medical Hydrology, Milan, was undertaken in order to clarify the relationship between osteoporosis and osteomalacia (a subject of much controversy) and to evaluate the role of the adrenal cortex in the metabolism of protein in these osteopathies. It was carried out on nineteen cases of senile osteoporosis and ten cases of osteomalacia, nine subjects who showed no radiological evidence of decalcification serving as controls. Nearly all the 38 subjects were women, ranging in age from 54 to 93 years, who had been admitted to hospital suffering from chronic disease; all patients in whom there was clinical evidence of hepatic or renal insufficiency were excluded from the study.

Estimation of the serum concentrations of calcium, phosphorus, alkaline phosphatase, total protein, albumin, alpha, beta, gamma, and total globulin, and measurement of the urinary excretion of calcium, 17-ketosteroids, and 11-corticosteroids all gave results which fell within the normal range. The conclusion is therefore drawn that "too sharp a distinction . . . has been made between osteoporosis and osteomalacia".

[This investigation failed to achieve its aims. No balance studies were performed and no details of intake or excretion of the various metabolites are given. The method employed can give only very limited information, which is insufficient to justify the authors' conclusion.]

P. D. Bedford.

Osteoporosis and Compression Fractures from Prolonged Cortisone and Corticotropin Therapy. EISENSTADT, W. S., and COHEN, E. B. (1955). *Ann. Allergy*, **13**, 252. 2 figs, 12 refs.

The authors report from the Mount Sinai Hospital, Minneapolis, two cases of perennial bronchial asthma in the first of which severe lumbar pain appeared after 3 years' continuous therapy with cortisone (dosage 50 to 100 mg. per day) or ACTH gel (20 to 40 mg. per day). Radiological examination revealed osteoporosis of the lower dorsal and lumbar vertebrae and pelvis, and multiple compression fractures of the lumbar vertebrae; the mean urinary calcium excretion was 194 mg. per day. The second patient had received maintenance doses of 50 to 75 mg. cortisone per day. After 3 years of this treatment the urinary calcium level was 474 mg. per day,

and radiographs of the spinal column showed early osteoporotic changes. In this case the patient had not complained of pain.

In both cases combined treatment with oestrogens and androgens was started at once. In the first patient this was followed by the disappearance of the pains, but the radiological picture remained unchanged; no results are reported for the second case. [The cortisone treatment was apparently continued in both patients, although the authors do not say so.] *H. Herxheimer.*

Corticotropin and Cortisone in Rheumatoid Arthritis. Clinical and Experimental Investigations. [In English.] FISCHER, F. (1955). *Acta med. scand.*, **152**, Suppl. 305, 1. 58 figs, bibl.

Cortisone in Experimental Histoplasmosis. VOGEL, R. A., MICHAEL, M., and TIMPE, A. (1955). *Amer. J. Path.*, **31**, 535. 3 figs, 10 refs.

Other General Subjects

Haemorrhage from the Digestive Organs during Treatment with Phenylbutazone. (Les hémorragies digestives au cours des traitements par la phénylbutazone.) COSTE, F., ANTOINE, B., and RAMPON, S. (1955). *Bull. Soc. méd. Hôp. Paris*, **71**, 100. 4 figs, 11 refs.

Four cases of gastro-intestinal haemorrhage following the administration of phenylbutazone are reported.

(1) In the first the patient had an extremely painful neuralgia in the left cervico-brachial region (subsequently shown to be due to neoplastic destruction of a cervical vertebra). Treatment, which included 500 mg. phenylbutazone given by intramuscular injection daily, produced much relief of the pain, but after 2 weeks the patient developed severe melaena, shock, and severe anaemia, which persisted in spite of blood transfusions. After a haematemesis 2 weeks later, gastric and duodenal ulcers were demonstrated radiologically and the patient died after gastrectomy.

(2) The second patient was treated for rheumatoid arthritis with phenylbutazone in a daily dose of 400 mg. by mouth for 11 days, followed by 600 mg. daily for another 2 weeks. This improved the condition considerably, but was followed by a haemorrhage of fresh blood per rectum which stopped immediately on withholding phenylbutazone. Proctoscopy and radiological examination of the gastro-intestinal tract revealed no abnormality. Two weeks later aspirin was given for a recurrence of the arthritic pains and a similar haemorrhage occurred without any subsequent ill-effects.

(3) The third patient developed melaena after receiving phenylbutazone intramuscularly for lumbar osteoarthritis in a dose of 1 g. every 2 days for 20 days; it was not possible to determine the source of the haemorrhage.

(4) The fourth patient was treated for sciatica with phenylbutazone in a daily dose of 800 mg. by mouth. After 10 days of treatment blood appeared in the stools and the patient complained of severe gastric pain. X-ray examination showed signs of gastritis which cleared up when treatment with phenylbutazone was stopped.

In an attempt to elucidate the effect of phenylbutazone on the gastro-intestinal tract the stools of 41 patients suffering from various types of rheumatic and arthritic conditions were tested for blood by the amidopyrine method after oral treatment with phenylbutazone in daily doses of 0·4 to 1 g. for an average period of 49 days. Whereas in all cases the test had given negative results before treatment, a positive result was obtained repeatedly after treatment in fifteen cases and intermittently in eleven others. The occurrence of blood appeared to be related to the duration of treatment in most cases, but in some blood was present after a relatively short course of treatment.

Although the authors admit that pre-existing factors may have determined the occurrence of severe haemorrhage in the four cases described, it would appear probable from their later experimental findings that some action of phenylbutazone was at least a contributory factor. *R. Wien.*

Clinical and Experimental Studies on the Pathogenesis of the Gastric Lesions (Ulcers, Haemorrhages) provoked by Phenylbutazone. (Considérations cliniques et expérimentales sur la genèse des lésions gastriques (ulcères, hémorragies) provoquées par la phénylbutazone.) BONFILS, S., HARDOUIN, J. P., RICHIR, C., DELBARRE, F., and LAMBLING, A. (1955). *Bull. Soc. méd. Hôp. Paris*, **71**, 114. 4 figs, 7 refs.

It was found by the authors that gastric lesions could be produced experimentally in the rat by giving daily doses of 100 mg. phenylbutazone per kg. bodyweight, either by mouth or by injection, after ligating the pylorus. These lesions, which appeared about the sixth day, took the form of small, diffuse ulcers, often haemorrhagic, originating in the mucous glandular layer and extending towards the surface. Concomitantly there was a considerable fall in the hydrochloric acid content of the gastric juice, resulting in some cases in achlorhydria. Analysis of the gastric juice showed that little phenylbutazone was excreted by this route.

The lesions produced clinically and experimentally by phenylbutazone are contrasted with those associated with the clinical administration of cortisone and ACTH. The latter occur in the duodenum rather than the stomach, and are the result of increased gastric secretion and hyperchlorhydria, whereas the appearance of the experimental lesions suggests that phenylbutazone has a direct toxic action on the gastric mucosa. There is thus little support for the suggestion that the gastric effects of phenylbutazone treatment are due to stimulation of the adrenal cortex. *R. Wien.*

Contribution of the Study of Twins to the Problem of Rheumatism. (Beiträge der Zwillings-Forschung zum Rheuma-Problem.) CLAUSSEN, F. (1955). *Z. Rheumaforsch*, **14**, 145. 30 refs.

Among the patients included in a large survey of rheumatic disease carried out in Germany in 1936–37, there were 73 pairs of twins. In fourteen of the 43 pairs of identical twins both members suffered from rheumatic disorders, whereas of the thirty pairs of non-identical

twins in only two were both members affected. In the author's view these findings demonstrate the fortuitousness of rheumatic infections and the importance of trigger mechanisms. The more frequent involvement of both twins in the identical series is taken as affording evidence of a hereditary disposition to rheumatic disorders. Further analysis showed that even the type and progress of the disease was influenced by heredity. The time interval between the onset of rheumatic disease in two members of a pair was sometimes many years and in only a few cases did the onset coincide. Re-examination of 28 of the pairs in 1951–52 showed that one further pair in each group had become concordant.

G. W. Csonka.

Ocular Manifestations of Chronic Rheumatism. (Les manifestations oculaires du rhumatisme chronique.) BONNET, P., and THIERS, H. (1954). *Rev. Rhum.*, **21**, 476.

Ocular manifestations of chronic rheumatism are similar to those due to any evolutive infection. They are described in children's chronic rheumatism, evolutive polyarthritis, and ankylosing spondylarthritis. In all cases, iridocyclitis may be torpid and revealed by routine eye examination. *S. Vallon.*

Rheumatism and Eye-Diseases. [In Hungarian.] SZALÓCZY, K. (1955). *Szemészet*, **92**, 56.

Stevens-Johnson Syndrome and Granulocytopenia after Phenylbutazone. STEEL, S. J., and MOFFATT, J. L. (1954). *Brit. med. J.*, **1**, 795. 4 refs.

Rheumatic Diseases in the Works of Rufus of Ephesus. (Las afecciones reumaticas en la obra de Rufo de Efeso.) RUIZ MORENO, A. (1955). *Arch. argent. Reum.*, **18**, 11.

Cardiovascular System and Phenylbutazone Therapy, Experimental and Clinical Observations. (Apparato cardiovascolare e terapia con fenilbutazona.) CURZIO, A., and FRANCO, G. (1955). *Reumatismo*, **7**, 286. 8 figs, 11 refs.

Eye Disorders in the Clinical Picture of Rheumatism. (Über Augenerkrankungen im Symptomenbilde des Rheumatismus.) MYLIUS, K. (1955). *Z. Rheumaforsch.* **14**, 222.

Deoxycortone and Salicylates in the Treatment of Rheumatic Diseases. (Desossicorticosterone e salicilici nel trattamento delle malattie reumatiche.) SCHIAVETTI, L., and FERRARIS, F. (1955). *Rif. med.*, **69**, 901. 1 fig.

Ann. rheum. Dis. (1956), **15**, 115.

MEASUREMENT OF BONE DENSITY*

BIAS AND VARIATION DUE TO RADIOGRAPHIC AND PHOTOMETRIC TECHNIQUES

BY

DONALD MAINLAND†

From the Department of Medical Statistics and the Study Group on Rheumatic Diseases, New York University College of Medicine

(RECEIVED FOR PUBLICATION MAY 8, 1956)

Conflicting Opinions Regarding Densitometry

"Bone density is an important and little-investigated variable about which we should like to know more" (*American Journal of Physical Anthropology*, 1954). Here an anthropologist echoed a nutritionist (*Nutrition Reviews*, 1952) regarding photoelectric densitometer estimates of *x*-ray opacity expressed as thickness of an aluminium or ivory step-wedge (or bone slabs) exposed on the same film as a living subject's hand or other region. This method has been used to measure bone changes in arthritis (Bywaters, 1948; Engström, Wegstedt, and Welin, 1948; Engström and Welin, 1949) and other diseases (Mortimer, Levene, and Rowe, 1937). Its most extensive development (Brown and Birtley, 1951; Mack, 1950; Mack, Brown, and Trapp, 1949; Mack, O'Brien, Smith, and Bauman, 1939; Mack, Trapp, and Brown, 1950) has culminated in the formation of a Bone Density Centre (Brown, 1953; McFarland, 1954) to which films can be sent for rapid assessment by an elaborate and ingenious equipment, and the description of this technique has been so convincing as to prompt the suggestion that it might take the place of calcium balance analyses (Hoobler, 1950).

Many radiologists and rheumatologists, however, remain unconvinced, chiefly because of the variation produced in films by *x*-raying and processing, and the masking of bone mineral loss by overlying soft tissue (and by internal organic matter). These problems arose in two current studies in this department: a search for age differences in bone density in healthy adults, and a seriatim comparison of densities in rheumatoid arthritics, some treated by cortisone and some by other methods. Experiments to determine the effects of technique (*x*-raying, processing, and photometry) were conducted on cadaver bones and on ivory wedges used as a substitute for bone to avoid variability due to cancellous structure. Several medical radiologists kindly commented on these experiments as follows:

(1) A study of the causes of variability in films should discuss *x*-ray absorption factors, such as atomic number of absorber, energy of radiation, filtration, and scattering.

(2) The effects of technique factors have been known, in general, for many years. Therefore such an investigation is unnecessary.

(3) Because radiologists' scepticism concerns bone density measurements on living subjects, cadaver bone tests can contribute nothing towards overcoming that scepticism.

Since these opinions are held by workers experienced in bone radiology they deserve consideration by anyone who contemplates using densitometric estimates for either clinical or research purposes.

The masking of mineral loss by soft tissue has been well attested (Ardran, 1951; Lachmann and Whelan, 1936; Shackman and Harrison, 1948). Nevertheless, visual assessments of bone shadows continue to be made because a change in mineral content, if large enough (*e.g.* 20 per cent. for some bones; Lachmann and Whelan, 1936), causes a change in bone shadow density. To those who distrust the eye, even when it is aided by a "standard bone" exposed with every arthritic's hand (Steven, 1947), densitometry offers a desirable substitute for three reasons:

(1) It is more objective than the eye;

(2) It is more sensitive than the eye;

(3) By expressing bone shadow density as equivalent thickness of a standard substance exposed on the same film, it corrects, to a considerable extent, for interfilm differences in overall density.

* Research supported in Canada by grants to the Dalhousie University Anatomy Department from the John and Mary R. Markle Foundation and the National Research Council of Canada; in New York by the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service (PHS Grant No. A-104).

† Address: 550 First Avenue, New York 16, N.Y.

A correction for interfilm differences in soft tissue is made also, usually by subtracting from the bone density a quantity derived from readings of soft tissue thickness and density on a film taken at right angles to the bone density film; but this cannot fully undo the masking effect of soft tissue, and densitometry must be regarded as giving an indirect and perhaps far from accurate, estimate of phenomena inside the bone. A similar statement could, however, be made regarding many quantitative biochemical and physiological methods used in clinical and experimental work, and this is not considered sufficient reason for rejecting a method, for failing to find its inherent technical biases and variability, or for attempting to reduce these defects.

Information Required

Four basic questions regarding bone densitometry may be posed:

(1) How far does the transformation into wedge thickness compensate for the effects of technique differences?

(2) What controllable factors could cause bias, *e.g.* a spurious difference between films from the same person on two occasions?

(3) How much bias?

(4) If this bias were eliminated, how much variation would remain?

These questions cannot be answered, even "in general", by the numerous published statements regarding the effects of *x*-raying and processing techniques on direct photometer readings of shadows not transformed into wedge thickness (Kieffer and Seideman, 1946; Mattsson, 1951; Mees, 1954; Morgan and Van Allen, 1949; Wilsey, 1934). Specific answers seem to be available only in reports from which numerical values cannot be transferred to current research on bone because they were obtained on tooth slabs nearly 20 years ago (Hodge, Bale, Warren, and Van Huysen, 1935; Hodge, Van Huysen, and Warren, 1935, 1937, 1938; Hodge, Van Huysen, Wilsey, and Warren, 1936; Hodge and Warren, 1936; Hodge, Wilsey, Van Huysen, and Warren, 1937).

Such a laboratory method cannot be evaluated by discussing *x*-ray physics or by applying the criteria of clinical radiology and, since repeated filming of the same object is necessary, cadaver bones must be used. Each investigator should, of course, test the method in the conditions that will prevail when he uses it; but a statement of some of the chief results obtained in this laboratory* will show what factors should, in any case, be controlled.

* A detailed report will be available on request.

Materials and Methods

The objects, on 10 × 12-in. no-screen films, were human bones (calcaneus, finger phalanx, distal ends of radius and tibia), aluminium, and ivory step-wedges. Exposure: table-top at 72 in. from 1·2-mm. focal spot of rotating-anode tube; 100 ma., 0·3 sec., as in concurrent living-subject hand studies. Development without agitation permitted estimation of maximal heterogeneity effects due to products of developing.

Seven factors were tested, each at two levels, some of them purposely differing more than was customary:

(1) *Wedge Position.*—Vertical (VW) versus Transverse (TW).

(2) *Kilovoltage.*—High (HK, 65 kv.p.) versus Low (LK, 50 kv.p.), as used for adults' and children's hands respectively.

(3) *Film Position in Processing.*—The end towards the head of the *x*-ray table was called the "top". Top uppermost in hanger (TU) versus Bottom uppermost (BU).

(4) *Speed of Developing.*—Quick (QD, 5·5 min. in fluid initially fresh but unreplenished during the developing of 56 pairs of films) versus Slow (SD, 7–8 min. in the same fluid weakened by films of another experiment).

(5) *Fixation Time.*—Short (SF, 20 min.) versus Long (LF, 2–3 hours).

(6) *Washing Time.*—Short (SW, 1 hour) versus Long (LW, overnight or 6–8 hours by day).

(7) *Drying Method.*—Warm (WD, in film-dryer) versus Cool (CD, in the open room).

The design was a simple factorial, widely used in biology (Finney, 1955), chemistry (Youden, 1951), and industry (Brownlee, 1949), and highly recommendable for testing *x*-ray techniques. To include all possible combinations, $2^7 = 128$ films were used, but to show minimal interfilm variation two films (*A* immediately followed by *B*) were made for each combination and processed together—a total of 256 films. The films were read between cellulose sheets, 0·01 in. thick on a Photovolt transmission densitometer (photometer models 500A and 501A).

Results

The figures shown below illustrate what was found on bones, but were obtained on an ivory wedge (9·93 mm. ivory; mean equivalent aluminium= 4·25 mm.—a density similar to that of several hand bones in life).

The results are abbreviated thus:

"In HK, TW>VW, 3·2 per cent. (4·3), $P<0·001$" indicates that, with the higher kilovoltage, the mean density (in mm. aluminium) with wedges transverse exceeded the mean density with wedges vertical by 3·2 per cent. of the latter. *P*, the probability of such differences occurring by chance, is less than one in a thousand. The figure 4·3 is the upper (95 per cent.) confidence limit for the difference, to

show that the "true" value of the difference, revealed by a much larger experiment, might have approached 4·3 per cent., but there is a 95 per cent. probability that it would not have exceeded that value.

Wedge Position.—In HK, TW>VW, 3·2 per cent. (4·3); $P<0·001$.
In LK, TW>VW, 1·5 per cent. (2·4); $P<0·01$.

Kilovoltage.—In SW, HK>LK, 1·1 per cent. (2·2); $P=0·05–0·02$.
In LW, LK>HK, 0·5 per cent. (1·6); $P=0·4–0·3$.

Film Position.—In SF, TU>BU, 2·3 per cent. (3·4); $P<0·001$.
In LF, TU>BU, 0·4 per cent. (1·4); $P=0·6–0·5$.

Fixation Time.—In TU, SF>LF, 1·0 per cent. (2·1); $P=0·1–0·05$.
In BU, LF>SF, 0·9 per cent. (2·0); $P=0·1–0·05$.
(For tibia as mm. ivory, in SW, LF>SF, 4·4 per cent. (8·0); $P=0·02–0·01$.)

Washing Time.—In HK, SW>LW, 0·2 per cent. (1·3); $P=0·8–0·7$.
In LK, LW>SW, 1·5 per cent. (2·6); $P<0·01$.

Drying Method.—In TU, CD>WD, 1·0 per cent. (2·1); $P=0·1–0·05$.
In BU, WD>CD, 1·7 per cent. (2·8); $P<0·01$.

The ivory wedge was not measured in terms of aluminium in the slowly developed (SD) series, but in radius and tibia the mean densities were significantly greater in SD than in QD films ($P<0·01$). The QD series (128 films), however, showed no influence of progressively weakening developer on bone density expressed as wedge thickness.

Each of the seven factors, under one or more conditions, had a statistically significant effect ($P<0·05$), and, although the effect of each factor may seem small, the bias produced by their summation would have considerable practical significance also.

Because of a radiologist's question, it is perhaps desirable to point out that the foregoing figures do not "make a direct statistical comparison of factors, such as kilovoltage and fixation time, that are completely independent", or any other kind of comparison between such factors. The experiment was designed to answer practical questions, such as: "If variation in one factor causes bias, is it possible to avoid rigid control of this factor by standardizing another one at a level where the first factor can fluctuate without causing bias?"

Estimation of residual variation (for the same ivory shadow as above) with all seven factors constant but developer heterogeneous as here, gave the following results:

(1) In random pairs of films, each read once, the greater density estimate would, in about 95 per cent. of pairs, exceed the smaller by less than 6·52 per cent. of the latter.

(2) If there were no densitometer reading variation, this value would be 4·95 per cent. Therefore the actual photometry, conducted by nine strict operating rules (specified in the longer report) needs little improvement.

(3) Expressed in the same terms, minimal interfilm variation (between *A* and *B* films), without reading variation, would be 4·37 per cent.

Discussion

The residual variation is attributable partly to unavoidable fluctuations (*e.g.* of voltage and the timing mechanism) during exposure, and probably largely to a lack of uniformity in the different parts of the developer. This also is difficult to rectify, except with small films, and it is possible that the 6·52 per cent. variation mentioned above could not be materially reduced.

If, however, an investigator found that he could attain this degree of precision on cadaver material, he would probably feel justified in carrying out further tests on living subjects, as by duplicate films of healthy persons at an interval of several weeks; but he should note that the constancy of the seven factors (as well as milliamperage and exposure time) requires a more rigid procedure than has previously been thought necessary (Brown, 1953). Indeed, it appears doubtful if reliable densitometric results can be obtained unless films are exposed and processed by a research-trained technician under conditions of an investigational laboratory.

Summary

Measurement of bone shadow density by photoelectric cell, with transformation into equivalent thickness of a standard substance (aluminium, ivory, or bone) exposed on the same film, is a useful objective substitute for visual assessment, even if, owing to the masking effect of soft tissue, it cannot claim to indicate bone mineral changes accurately.

Before densitometry can be used confidently, however, it should be strictly evaluated as a laboratory method; and, although much has been published about the effects exerted on direct photometer readings by technique variation in *x*-raying and processing, it is not known precisely how far these effects are negatived by transformation of bone shadow readings into thickness of a standard substance.

Experiments of the simple two-level factorial type, in which cadaver bone shadows and ivory shadows were expressed as aluminium thickness, revealed that, with time and milliamperage constant, each of the seven factors tested—wedge position, kilo-

voltage, film position in processing, speed of developing, fixation time, washing time, and drying method (in a warm dryer or in an open room)—could introduce bias, *e.g.* a spurious difference between two films from the same subject.

When these factors were held constant, the residual variation was low enough to justify applying the method to living subjects, but to fulfil the necessary requirements it appears essential that a research-trained technician should work under the conditions of an investigational laboratory.

I am greatly indebted to Dr. Pauline B. Mack for information and encouragement in this research, and for donation of the ivory wedges; to Mrs. R. B. Mainland for the radiography; and to Mrs. H. H. Wertheimer for the densitometry.

REFERENCES

American Journal of Physical Anthropology (1954). **12**, 265.
Ardran, G. M. (1951). *Brit. J. Radiol.*, **24**, 107.
Brown, W. N. (1953). "Instructions for Exposing and Developing X-ray Films for Bone Density Evaluation." Pennsylvania State College, Pa.
——, and Birtley, W. B. (1951). *Rev. scient. Instrum.*, **22**, 67.
Brownlee, K. A. (1949). "Industrial Experimentation." Chemical Publishing Co., Brooklyn, New York.
Bywaters, E. G. L. (1948). *Clin. Sci.*, **6**, 281.
Engström, A., Wegstedt, L., and Welin, S. (1948). *Acta radiol.*, **30**, 440.
——, and Welin, S. (1949). *Ibid.*, **31**, 483.
Finney, D. J. (1955). "Experimental Design and Its Statistical Basis." University of Chicago Press, Chicago.
Hodge, H. C., Bale, W. F., Warren, S. L., and Van Huysen, G. (1935). *Amer. J. Roentgenol.*, **34**, 817.
——, Van Huysen, G., and Warren, S. L. (1935). *Ibid.*, **34**, 523, 529, 678.
——, ——, —— (1937). *Ibid.*, **37**, 529.
——, ——, —— (1938). *Ibid.*, **40**, 108, 269.
——, ——, Wilsey, R. B., and Warren, S. L. (1936). *Ibid.*, **36**, 531.
——, and Warren, S. L. (1936). *Ibid.*, **36**, 391.
——, Wilsey, R. B., Van Huysen, G., and Warren, S. L. (1937). *Ibid.*, **37**, 385.
Hoobler, I. M. (1950). In "Nutrition in Relation to Health and Disease", p. 59. Proc. 1949 Annual Conference. Milbank Memorial Fund, New York.
Kieffer, J., and Seideman, R. M. (1946). *Science*, **104**, 596.
Lachmann, E., and Whelan, M. (1936). *Radiology*, **26**, 165.
Mack, P. B. (1950). *In* "Nutrition in Relation to Health and Disease", p. 30. Proc. 1949 Annual Conference. Milbank Memorial Fund, New York.
——, Brown, W. N., and Trapp, H. D. (1949). *Amer. J. Roentgenol.*, **71**, 808.
——, O'Brien, A. T., Smith, J. M., and Bauman, A. W. (1939). *Science*, **89**, 467.
——, Trapp, H. D., and Brown, W. N. (1950). *In* "The Biology of Human Starvation", ed. A. Keys, J. Brožek, A. Henschel, O. Mickelsen, and H. L. Taylor, vol. 2, p. 1081. University of Minnesota Press, Minneapolis.
Mattsson, O. (1951). *Acta radiol.*, **36**, 273.
McFarland, W. (1954). *Science*, **119**, 810.
Mees, C. E. K. (1954). "The Theory of the Photographic Process", rev. ed. Macmillan, New York.
Morgan, R. H., and Van Allen, W. W. (1949). *Radiology*, **52**, 832.
Mortimer, H., Levene, G., and Rowe, A. W. (1937). *Ibid.*, **29**, 279.
Nutrition Reviews (1952). **10**, 119.
Shackman, R., and Harrison, C. V. (1948). *Brit. J. Surg.*, **35**, 385.
Steven, G. D. (1947). *Annals of the Rheumatic Diseases*, **6**, 184.
Wilsey, R. B. (1934). *Amer. J. Roentgenol.*, **32**, 789.
Youden, W. J. (1951). "Statistical Methods for Chemists." Wiley, New York.

Mesure de la densité osseuse et écarts et variations dus aux techniques radiographiques et photométriques

RÉSUMÉ

La mesure de la densité de l'ombre osseuse à l'aide d'une cellule photo-électrique, avec transformation en épaisseur équivalente d'une substance standard (aluminium, ivoire ou os) éxposée sur le même cliché, est un suppléant objectif utile de l'examen visuel, même si, en raison de l'effet masquant des tissus mous, elle ne peut prétendre indiquer avec précision les altérations minérales de l'os.

Avant que l'on puisse utiliser la densitométrie avec confiance, il conviendrait qu'elle fût strictement évaluée en tant que méthode de laboratoire et, bien qu'on ait publié beaucoup de choses à propos de l'effet sur la lecture directe au photomètre des variations de technique radiographique et d'impression, on ne sait pas exactement jusqu'à quel point ces effets sont annulés par l'interprétation de l'ombre osseuse en épaisseur d'une substance standard.

Des expériences du type factoriel simple, dans lesquelles des ombres d'os de cadavres et des ombres d'ivoire furent exprimées en épaisseur d'aluminium, révélèrent que, avec le temps et l'intensité constants, chacun des sept facteurs vérifiés: position du coin, voltage, position du cliché durant l'impression, vitesse de développement, temps de fixage, temps de lavage et méthode de séchage (dans un sécheur chaud ou à l'air libre) pouvait introduire un écart, par exemple une différence trompeuse entre deux clichés d'un même sujet.

Quand ces facteurs furent maintenus constants, la variation résiduelle fut assez minime pour justifier l'application de la méthode à des sujets vivants, mais pour remplir les conditions requises il apparaît nécessaire qu'un technicien entrainé à la recherche travaille dans les conditions d'investigation de laboratoire.

Medida de la densidad ósea y desvios y variaciones debidos a procedimientos radiográficos y fotométricos

SUMARIO

La medida de la densidad de la sombra ósea de la ayuda de una célula fotoeléctrica, con transformación en espesor equivalente de una substancia de norma (aluminio, marfil o hueso), expuesta sobre el mismo clisé, es un substituto objetivo útil de la inspección, aún que, en razón del efecto enmascarante de los tejidos blandos, no puede pretender de indicar con precisión las alteraciones minerales del hueso.

Antes de poder emplear la densitometria con confianza, sería preciso averiguar estrictamente su valor como método de laboratorio. Aunque se haya escrito mucho respecto al efecto sobre la lectura fotométrica directa de las variaciones de técnica radiográfica y de revelamiento, no se sabe todavía exactamente hasta que punto estos efectos se ven anulados por la interpretación de la sombra ósea en espesor de una substancia de norma.

Experimentos del tipo factorial simple, en que las sombras de huesos de cadáveres y sombras de marfil fueron exprimidas en espesor de aluminio, revelaron que, con el tiempo y la intensidad eléctrica constantes, cada de los siete factores estudiados: posición del cuño, voltage, posición del clisé durante su manipulación, velocidad del revelamiento, tiempo de la fijación, tiempo de lavar y método de secar (en un secador caliente o al aire libre) podía causar un desvio, por ejemplo una diferencia engañadora entre dos clisés del mismo sujeto.

Al mantener constantes todos estos factores, la variación residual fué suficientemente pequeña para justificar la aplicación del método a sujetos vivos, pero para satisfacer las condiciones requeridas parece necesario que un auxiliar instruido en métodos científicos trabaje en condiciones de investigación de laboratorio.

Ann. rheum. Dis. (1956), **15**, 119.

ANKYLOSING SPONDYLITIS

THE LITERATURE UP TO THE CLOSE OF THE NINETEENTH CENTURY

BY

D. O'CONNELL

London

(RECEIVED FOR PUBLICATION FEBRUARY 9, 1956)

Ankylosing spondylitis, a disease causing pain and stiffness referable to the spine and large joints, has affected the human race for ages past. Traces are to be found in the skeletons of the earliest Egyptians and there is no reason to believe that it was then a new disease. Ruffer (1918) found evidence of true ankylosing spondylitis amongst the many cases of spondylitis deformans he came across dating back as far as 5000 B.C. Smith (1908) differentiated between the two diseases in his investigations of Egyptian and Nubian skeletons and found a fairly high incidence of the former in the graves he opened; interesting illustrations can be found in his atlases in the British Museum. Though it is an uncommon disease, it does cripple young men, and I therefore think it remarkable that references in the literature are so rare, at least up to the final quarter of the nineteenth century.

It is doubtful who was the first to describe the syndrome, but I am satisfied that the first adequate clinico-pathological account was given long before the generally accepted authors published their findings. Up to the present time, the credit has been distributed between such writers as Fagge (1877), Sturge (1879), von Bechterew (1892), Marie (1898), Leri (1899), and Strümpell (1897). In the 1880s many others added their cases, notably Clutton (1883), Bradford (1883) in the U.S.A., and Davies-Colley (1885) of Guy's.

As I shall show, to give credit to one or to divide it between a number of these eminent men would be unfair to physicians and surgeons of the earlier 1800s and before. Though there is little to be found in the literature, excellent papers have been written; a résumé of the historical data is given below.

The earlier writers are vague and the famous Caelius Aurelianus (5th cent. A.D.) in his *de Ischiadicis et Psoadicis* includes a great number of conditions with similar symptoms. His *Psoadicus* (probably Pliny's *Psoadicus Dolor*) corresponds in part to our disease; he refers to the attachments of the lower vertebral column and notes a stiff woodenness:

> The patient is seized by pain in the nates, moves slowly, and can only bend or stand erect with difficulty (Mettler, 1947).

Sydenham in the latter half of the seventeenth century was one of the first to give a reasonable description of rheumatism; he divided it into three kinds, the second two following from the first:

(1) Acute rheumatism or rheumatic fever.
(2) Chronic rheumatism or modern rheumatoid arthritis.
(3) Rheumatic lumbago.

Of the third type Sydenham writes (trans. J. Pechy, 1696):

> It is properly called the Rheumatical Ach of the Loins, a violent Pain being fixed there, and stretching sometimes to the *Os Sacrum*.... Upon which account I have been heretofore mistaken, thinking it was produced from Gravel sticking in those Parts; whereas in truth it owed its rise to the peccant and inflamed Matter of the *Rheumatism*, which afflicts indeed only those Parts, the rest of the Body being untouched. This violent pain continues as the other Species [Chronic Rheumatism] if it be not cured after the same manner, grievously afflicting the poor Patient, so that he cannot lie in his Bed, but is forced to leave it, or to sit upright, rocking himself continually.

The description is a clinical one only, with no allusion to *post-mortem* dissection, but this is typical of Sydenham who was essentially a clinician. It was not until the following century that Morgagni developed the system of correlating clinical and *post-mortem* findings.

In 1691 Bernard Connor used as subject for his M.D. thesis at the University of Rheims a skeleton which he had found in a graveyard. This showed

an advanced stage of the disease (Fig. 1). Connor gave a full and detailed description, and (1695) reconstructed with fair accuracy the probable symptoms, making a few wild shots at the aetiology.

Fig. 1.—Skeleton described by Bernard Connor (1695)

The following are some excerpts from Connor:

> As to the crooked and bending Shape of the Skeleton it is reasonable to suppose that it proceeded from the first Formation of the Foetus in the Womb, from the Eggs not having sufficient Room, or being accidentally pressed by some Abscess in the Womb or elsewhere, so that the Carina of the Backbone instead of running straight, was bent into a Circle and kept the same Figure when at full growth that these Bones had taken when soft and tender.
>
> From the Construction of the Parts it necessarily follows that this Body must have been immovable . . . breathing achieved by diaphragmatic Movement . . . Possibly the Foramen Ovale might continue open, and that by it and the Arterial Canalis the Blood might pass from the Cava to the Aorta, but a part of it passing through the lungs.

Whatever his shortcomings, Connor thus published the first pathological description of a case of ankylosing spondylitis and if his aetiological ideas are amusing to us, his reconstruction of the symptoms caused was logical.

Lyons (1831), writing to the *Lancet*, gives an interesting study of a man aged 36 who had had a 7½ years' history. Pain and stiffness had spread from his elbows and knees to his back, so that in 15 months he was unable to bend because of a rigid spine. Lyons noted that the local pain ceased as each part became fixed, a point now usually ignored or unrecognized. He noted no inflammatory changes. He referred to some totally ankylosed museum specimens, including one in Paris, one in the Hunterian Collection, and one in Trinity College, Dublin. That at Dublin (Fig. 2, opposite) had been the subject of an excellent description in a letter from the Bishop of Cork to the Earl of Egmont (1741). Lyons distinguished the condition of each of these skeletons from that of his own patient. These cases were in fact examples of myositis ossificans progressiva, and his patient was obviously afflicted by a different disease. He tried to arrange admission to a Dublin Hospital with an eye to an eventual *post-mortem* examination and pressed his case by noting that Hunter had given £100 for his skeleton which had had no history attached. Here was one, well documented, which with a little arrangement might be had for nothing! He placed a duty on the Dublin members of the profession to see to this and the man was demonstrated in Dublin shortly afterwards. However, the patient, a Manxman, decided, with excellent judgment, that if he wished to be buried according to custom he had better return to the Isle of Man. This he did and when he died, in order to outwit any "resurrectionists", his friends, in answer to his last wishes, cut up his body into small pieces with "saws and sledges". However, they did not reckon with the persistence of Lyons and his friends, for a year or so later the bones found their way back to the Museum of the Royal College of Surgeons of Ireland and the skeleton was reconstructed. The specimen no longer exists, but there is a description by Houston (1840) in the Museum Catalogue.

About the same time Adams and others in Dublin described ankylosed vertebrae, and Adams (1857), in his *Treatise on Rheumatic Gout*, described typical pain and stiffness and the postures these lead to.

He recognized the apparently healthy vertebral

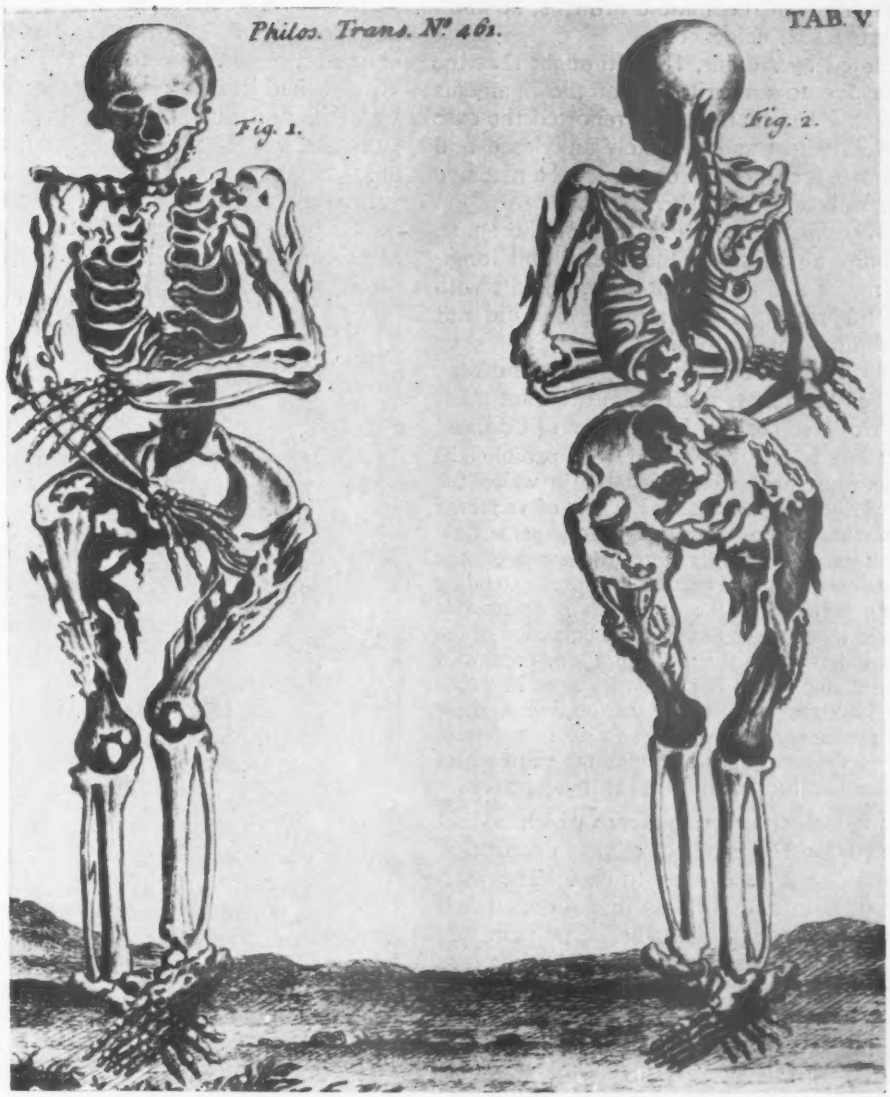


Fig. 2.—Skeleton at Trinity College, Dublin, described by Robert, Bishop of Cork (1741).

body, and the intact disks with the accompanying bony changes in the ligaments. He included a drawing of an affected odontoid peg (Fig. 3) showing where the ligamentous attachments near the apex were partially calcified, giving the appearance of a "Phrygian cap".* He noted that the proper function of the marrow was not interfered with.

When Adams addressed the medical section of the British Association at Bristol in 1836, he noted that in "chronic rheumatic arthritis" in women the small joints were affected, while in men it attacked the central joints. Although he thought that the disease

Fig. 3.—Drawing of odontoid peg by Adams (1857

* Cf. Ruffer (1918).

was only a variant of rheumatoid arthritis, he knew of the differing sex incidence.

Todd (quoted by Adams, 1857) thought that the disease was due to an irritation of the ligaments rather than to inflammation, and reported the case of a girl of 25 who was completely ankylosed and unable to move, for whom he constructed a machine to hoist her into and out of bed.

Hare (1849), writing on curvature of the spine, described bony ankylosis of the lateral and longitudinal ligaments and of the apophyseal joints with fixation of the ribs to the vertebrae, but did not draw any clinical conclusions.

Brodie (1850), who described Reiter's syndrome a life-time before Reiter, put into print what must surely have troubled the inquisitive mind of Connor:

> Every one who is conversant with pathological museums must have seen specimens in which the bodies of a greater or smaller number of vertebrae are firmly ankylosed, there being at the same time a deposit of bony matter here and there on the surface adhering to the bone beneath, and extending from one vertebra to the other. It is reasonable to suppose that such a change in the condition of the spine must have been the result of a long-continued chronic inflammation; but in no instance in which I have had the opportunity of observing these morbid appearances, have I been able to ascertain what were the symptoms by which the existence of the disease had been marked in the living person.

He then went on to describe a case which he had observed in 1841. His excellent clinical description might be that of a case seen to-day. The man complained of pain and stiffness in the dorsal and lumbar spine, buttocks, and thighs. The pain was frequently induced by sneezing, "which therefore he completely avoided". One knee joint was affected and the man also had iritis. The onset had been gradual and he had had remissions and exacerbations. Brodie treated him with mercury, iodides, and sarsparilla, and the disease gradually burned itself out over a period of years, so that eventually the patient was left without symptoms except for "a rigid and inflexible spine".

Wilson (1856) described the case of a young labouring woman, admitted to the Baltimore Almshouse, who over a period of 10 years gradually stiffened from head to foot except for the lower jaw and the ribs. She only complained of pain periodically. Edwin Canton, assistant surgeon at Charing Cross Hospital, records rheumatic arthritis of the spine as a matter of course in some lecture notes of 1855. Adams (1857) had earlier quoted from some of his works.

Brodhurst (1858) showed the case of a young lieutenant, aged 25, who after gonorrhoea became completely stiff with an ankylosed spine. He showed a second case the next year of a man aged 46 who had also had gonorrhoea; his whole spine was stiff and diaphragmatic breathing was noted. Commenting on these cases, Brodhurst ascribed the ankylosis to "muscular rheumatism", a theory at variance with the currently accepted gonorrhoeal aetiology which lasted till near the end of the nineteenth century.

Hilton (1860), writing on pain, described how he treated a man with pain in the neck with continued and complete rest in the horizontal position. The patient was cured but was left completely ankylosed(!) and later died of tuberculosis.

Von Thaden (1863) described a case which he called "spondylitis deformans" in a young adult man, but as far as one can gather, this was a true case of ankylosing spondylitis.

In 1870, pieces of two spines showing bony ankylosis were pictured in the *British Medical Journal*, one human (from the London Hospital), and one equine (from the Royal College of Veterinary Surgeons). The bony appearance of the longitudinal ligaments and the fact that they did not dip into the disk spaces were noted.

We now arrive at the last quarter of the nineteenth century. Fagge (1877) and Sturge (1879) have lately been mentioned as being the original writers and are compared favourably with hitherto accepted authors, such as von Bechterew (1892-99), Marie (1898), and Strümpell (1897) from whose work Fig. 4 (opposite) is taken. Marie gave a valuable exposé which justifies his name being affixed to the disease.

Leri, his pupil, completed his work by filling in the *post-mortem* details of the cases and wrote on his own account in the early twentieth century. It is interesting that von Bechterew's name is that perhaps most commonly associated with the condition; the reason for this remains a mystery unless it be because he was one of the brightest medical luminaries of his day. The cases he described were, at best, atypical examples of the disease as we know it to-day, exhibiting neurological features unfamiliar to us. It seems, from a translation of his work, that he thought that the fundamental lesion lay in the meninges rather than in the spine itself (von Bechterew, 1893, 1897, 1899). In his *post-mortem* notes, he describes the posterior nerve roots and the columns of Goll and Burdoch as being degenerated! I have never seen a case showing

Fig. 4.—Case described by Strümpell (1897).

neurological lesions apart from those due to associated disease such as disk herniation.

However, as I have shown earlier, all these authors were rather late on the scene. Nearly two centuries previously Connor had given a very full skeletal picture but had had no clinical opportunity, while in 1850 Brodie had shown the hand of the master. Lyons produced an early case which he followed, one might say, beyond the grave, giving descriptions of the clinical features to which Houston added the skeletal details. Sydenham and Caelius Aurelianus must also share the honour.

The available literature of the time spotlights these names, but each was probably one among many contemporaries who thought along the same lines. Even in the eighteenth and early nineteenth centuries and no doubt before, the average medical man knew of the disease, though he usually regarded it as an extension of chronic rheumatoid arthritis, very much as the Americans do to-day. William Clark (1813), in some manuscript notes on rheumatism in the Charing Cross Hospital Medical School Library, mentions affection of the loins, abdomen, chest, and neck, and warns that when the pain has gone the stiffness will remain. Non-venereal iritis as an associated disease has been rediscovered in recent years, but the men of the early nineteenth century were already familiar with it; for example, Rosas (1837) of Vienna classified rheumatic inflammations of the eye into scleritis, keratitis, internal ophthalmia, and generalized acute and chronic ophthalmia, and described twelve cases.

These early writings on ankylosing spondylitis show a fairly clear understanding of the disease, from which we have since progressed little.

REFERENCES

Adams, R. (1857). "A Treatise on Rheumatic Gout". Churchill, London.

Bechterew, W. von (1892). *Russki Wratsch*, 36 (*Cited as* "Wratsch No. 36" by Bechterew, 1897, 1899.)

—— (1893). *Neurol. Zbl.*, 12, 426.

—— (1897). *Dtsch. Z. Nervenheilk.*, 11, 327.

—— (1899). *Ibid.*, 15, 45-57.

Bradford, E. H. (1883). *Ann. Anat. Surg.*, 7, 279.

British Medical Journal (1870). 2, 39.

Brodhurst, B. (1858). *Medical Tms* (*Lond.*), n.s. 16, 551.

Brodie, B. C. (1850). "Diseases of the Joints", 5th ed. Longman, Brown, Green, and Longmans, London.

Caelius Aurelianus (5th cent. A.D.).

Canton, E. (1855). "Surgical and Pathological Observations", p. 32. Highley, London.

Clark, W. (1813). Manuscript—Charing Cross Hospital Medical School.

Clutton, H. H. (1883). *Trans. clin. Soc. Lond.*, 16, 232.

Connor, B. (1691). Thesis, Rheims.

—— (1695). *Philos. Trans.*, 19, 21.

Cork, Robert, Bishop of (1741). *Ibid.*, 41, 810.

Davies-Colley, N. (1885). *Trans. path. Soc. Lond.*, 36, 359.

Fagge, C. H. (1877). *Ibid.*, 28, 201.

Hare, S. (1849). "Practical Observations on the Prevention, Causes and Treatment of Curvatures of the Spine", 3rd ed. Churchill, London.

Hilton, J. (1860). *Lancet*, 2, 378.

Houston, R. (1840). "Catalogue of the Museum of the Royal College of Surgeons of Ireland", vol. 2.

Leri, A. (1899). *Rev. Médecine*, 19, 597.

Lyons, P. M. (1831). *Lancet* (1831-32), 1, 27.

Marie, P. (1898). *Rev. Médecine*, 18, 285.

Mettler, C. C. (1947). "History of Medicine." Blakiston, Philadelphia.

Rosas, W. (1837). *Lancet* (1836-37), 2, 191.

Ruffer, A. (1918). *J. Path. Bact.*, 22, 152.

Smith, G. Elliot (1908). "The Archaeological Survey of Nubia", Bulletin No. 2, p. 59, etc. (footnote to article by F. Wood Jones). National Printing Dept., Cairo.

Strümpell, A. (1897). *Dtsch. Z. Nervenheilk.*, 11, 338.

Sturge, W. A. (1879). *Trans. clin. Soc. Lond.*, 12, 204.

Sydenham, T. (1707). "The Practice of Physick", trans. W. Salmon, London.

Thaden, von (1863). *Arch. klin. Chir.*, 4, 565.

Wilson, H. P. C. (1856). *Medical Examiner* (*Philad.*), June, p. 537.

Ann. rheum. Dis. (1956), **15**, 124.

ACQUIRED RESISTANCE TO CORTICOTROPINS

BY

H. F. WEST*

Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases

(RECEIVED FOR PUBLICATION APRIL 6, 1956)

Corticotropin, which may be defined as a pituitary extract that will directly stimulate the adrenal cortex to secrete its predominantly "glucocorticoid" hormones, has been in general use for about 5 years. In spite of this, its use as a therapeutic agent has not been defined. There are two reasons for this state of affairs. The first is that most physicians have assumed that the administration of synthetic corticosteroids (*i.e.* cortisone, delta-1 cortisone, etc.) amounts to the same thing as stimulating the adrenocortex. In consequence they have used only the more easily administered form of treatment. There is little evidence yet to prove or disprove this assumption, but on theoretical grounds it is not justified. The second reason is that much difficulty has been experienced in inducing and maintaining a therapeutic level of adrenocortical stimulation. This has discouraged physicians in their use of corticotropin and has prevented any valid trials of its use as a therapeutic agent. A study of the effects of prolonged adrenocortical stimulation upon the course of rheumatoid arthritis and ankylosing spondylitis was begun at this centre 3 years ago. After 18 months the therapeutic results were encouraging (West and Newns, 1955), but since that time the study has been brought almost to a halt because of the failure of the available "highly purified" corticotropins to maintain adrenocortical stimulation in many patients. Most of the observations made on acquired resistance to corticotropin that are reported below were incidental to this study. Forsham (1955) stated that he had not found the commercially available "highly purified" corticotropin gels to induce refractoriness or hypersensitivity, it being well known that the earlier preparations (not oxycellulose purified) did so.

In this paper evidence is presented which shows that on prolonged administration the development of refractoriness to highly purified corticotropin is common. In addition to refractoriness allergic reactions may occur that are not always harmless. Maddock, Leach, Tokuyama, Paulson, Nelson, Janget, and Heller (1956) reported the induction in man of non-species specific antigonadotrophins after the injection of pituitary gonadotrophin, which have apparently neutralized the patients' own gonadotrophins. If this can occur with one type of pituitary extract it may occur with another (*i.e.* corticotropin). Evidence relating to this problem is presented and discussed. The question whether the adrenocorticotropic hormone itself is allergenic remains unsolved. The findings reported here have a direct bearing on this problem. The word allergen is used in this paper in its widest sense, since the nature of the altered reaction that often occurs with prolonged administration of highly purified corticotropin has not been investigated.

Materials and Methods

The corticotropins used were Armour's High Purity (H.P.) Acthar Gel; Wilson's purified corticotrophin; Organon's purified Cortrophin-Z; Crooke's Zinc Protamine ACTH; and Duracton (Nordic Biochemicals Ltd.). In addition, small quantities of Armour's experimental "improved" beef and pork H.P. Acthar Gel were used, and a small quantity of porcine corticotropin A_1, kindly supplied by Dr. H. B. F. Dixon (for details of the nature and preparation of this hormone, see Dixon and Stack-Dunne, 1955).

It will be apparent from what follows that the labelled potency of the commercial preparations (in units per ml.) was of little help in determining the right dose to use. The problems of the biological assay of corticotropic pituitary preparations for human use are complex (see Thompson and Fisher, 1953) and are not yet solved. It is likely that the assays will remain a problem until the arrival of chemically pure corticotropin makes them unnecessary. It is the purity rather than the potency of these extracts that is relevant to this paper. We need some knowledge of the purity of any foreign protein we are to inject. The makers of corticotropins provide no such information with their products. Information regarding the purity of a corticotropin could be conveyed

* Part-time Nuffield Research Fellow, University of Sheffield.

either by a statement of the physico-chemical methods employed in purification, or by a statement of the potency of the preparation in units per mg. protein. Dr. Thompson of Armour Laboratories, Kankakee, has kindly provided the following information about the potency of the H.P. Acthar Gel preparations used, in units (U.S.P. XV) per mg. protein solid:

P80001 (beef) approx. 10 units per mg. protein.
N31605, 32306, 33307 (pork) approx. 40 units per mg. protein.
Improved beef H.P. Acthar Gel approx. 40 units per mg. protein.
Improved pork H.P. Acthar Gel approx. 40-60 units per mg. protein.

No such assay* has been performed on Dixon and Stack-Dunne's corticotropin A_1, but from our limited experience it is by far the most potent corticotropin, per mg. protein, that we have used. Although purity can be equated with potency per mg. protein, it does not follow that allergenicity can be so equated too, because the nature (and allergenicity) of the contaminating protein may vary from preparation to preparation.

The degree of adrenocortical stimulation achieved was measured by the assay of 17-ketogenic steroids (17 KGS; Norymberski, Stubbs, and West, 1953) or 17-hydroxycorticosteroids (17(OH)CS; Appleby, Gibson, Norymberski, and Stubbs, 1955; Appleby and Norymberski, 1955) in 24-hr specimens of urine. These assays reflect the adrenals output of cortisol in all circumstances except the following:

(1) When cortisol-like corticosteroids are being administered; in this circumstance a deduction for their contribution to the urinary metabolites measured must be made.
(2) In the rare adreno-genital syndrome, when other assay methods are called for, such as that of Appleby and Norymberski (1955).
(3) In the presence of severe renal failure when all urinary and blood levels of metabolites are effected.

A study of 3,000 assays for 17 KGS and/or 17(OH)CS made at this centre has shown that the evidence of adrenocortical activity that they provide is always consistent with the clinical state of the patient (except of course in the circumstances enumerated above). In the past eosinophil counts and the excretion of 17-ketosteroids have been used to measure adrenocortical activity. Although both these measures do reflect the changes in adrenal cortisol output neither provides a sufficiently accurate measure for therapeutic purposes.

The routine procedure for treatment has been to administer by intramuscular injection a dose of corticotropin that will maintain a daily urinary output of 17 KGS or 17(OH)CS between 20 mg. and 40 mg.; the level aimed at depending upon the severity of the disease process at the time. Some of the charts reproduced below will show how difficult this is to achieve. Assays on 24-hr urine collections were made at approximately 5-day intervals until a constant stimulation at the required level was achieved. Thereafter assays were made monthly unless the patients' clinical state suggested that a rise or fall in stimulation had occurred. If a fall had occurred the dose was raised and further assays performed. Acquired resistance was assumed to have developed if the assays confirmed a major decline in stimulation. The completeness of all 24-hr specimens were checked by routine creatinine estimations and constant vigilance was maintained in the laboratory to avoid and detect any errors that might occur in the analytical procedures employed in the 17 KGS and 17(OH)CS assays.

A group of 51 patients, all suffering initially from severe rheumatoid arthritis or ankylosing spondylitis, was treated by continuous adrenocortical stimulation therapy:

For 1 month or more	51
For 6 months or more	42
For 12 months or more	28
For 24 months or more	14
For 36 months or more	2

Results

(1) Initially, in all 51 patients, the administration of corticotropin caused adrenocortical stimulation.

(2) 42 patients subsequently acquired resistance to one or more preparations of corticotropin:

to two preparations	13
to three preparations	7
to four preparations	3
to five preparations	1
to six preparations	1

It should be pointed out that these findings did not result from an experiment with six preparations of corticotropin given to 51 patients, but were the findings incidental to a therapeutic trial extending over 3 years during which time many different batches of corticotropin came and went. A distinction is made between the development of resistance to a particular preparation or batch and the possession (subsequently) of resistance to another preparation *ab initio*.

(3) 36 patients responded to a subsequent preparation after having acquired resistance to a previous preparation.

(4) Ten patients responded to a second preparation and subsequently developed resistance to it.

(5) Eight patients responded to a third preparation after having responded and then acquired resistance to two previous preparations.

Examples.—As the evidence for these findings includes more than a thousand steroid assays and almost as many sets of clinical assessments, it is obviously impracticable to present them in full.

* In the U.S.P.(XV) assay the corticotropin is given subcutaneously. The unit bears no direct relation to the international unit which is based on an intravenous assay. In the latter assay Dixon and Stack-Dunne (1955) found their corticotropin A_1 to have approximately 70 units per mg. protein.

Instead, a number of the records, chosen to illustrate the main findings, are depicted graphically below. As some readers will not be familar with the type of adrenocortical response usually seen after the injection of potent corticotropin, the first three figures illustrate the common findings after a single injection, after injections given 12-hrly, and after injections given on alternate days.

(1) A woman aged 38 with rheumatoid arthritis gave a typical response to a single intramuscular injection of 40 units H.P. Acthar Gel (Fig. 1). The urinary output of 17(OH)CS returned to the control level within 24 hrs.

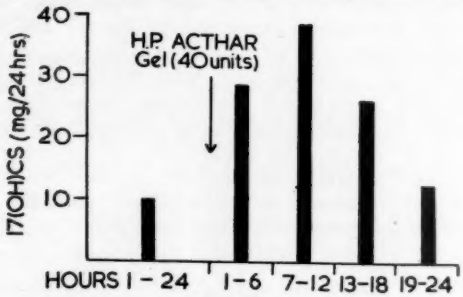


Fig. 1.—Response to a single injection of H.P. Acthar Gel in a woman aged 38 with rheumatoid arthritis.

(2) A woman aged 42 with rheumatoid arthritis was given 20 units of a long-acting preparation of corticotropin 12-hrly, which usually results in a progressive rise of adrenocortical activity (Fig. 2).

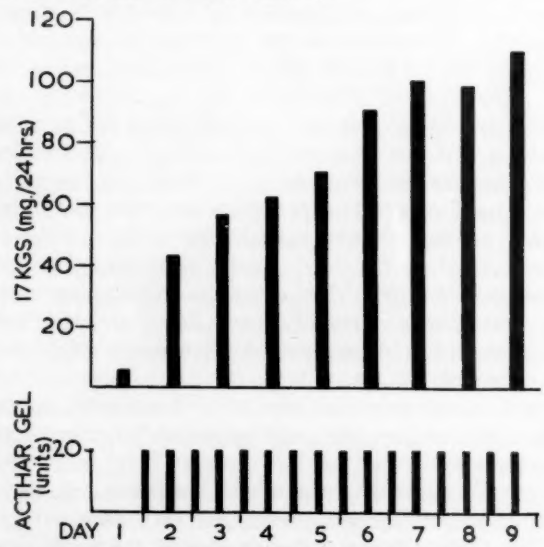


Fig. 2.—Response to 20 units of Acthar Gel given 12-hrly in a woman aged 42 with rheumatoid arthritis.

This rise is thought to be due to adrenal hypertrophy. An output of 110-120 mg. 17KGS or 17(OH)CS a day is the highest observed at this centre and may represent the upper limit of the adrenal capacity.

(3) In a man aged 45 with rheumatoid arthritis, once a steady level had been reached, the adrenals responded to injections on alternate days (Fig. 3).

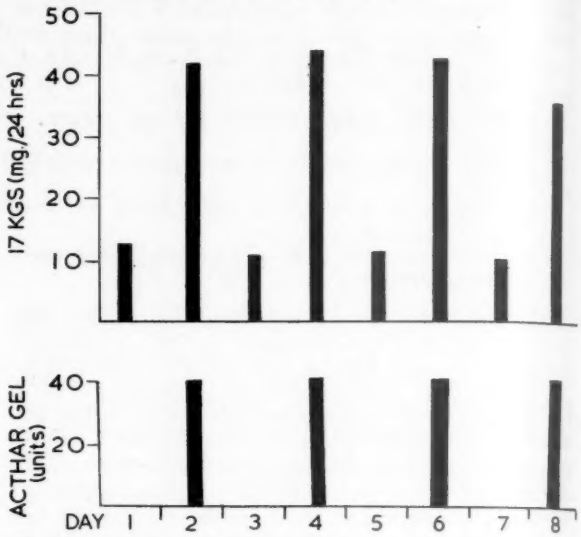


Fig. 3.—Response of adrenals to injections on alternate days in a man aged 45 with rheumatoid arthritis.

(4) A young man aged 15 with rheumatoid arthritis was observed for 3 years. Fig. 4 (opposite) shows how observations that reflect the degree of adrenocortical activity vary in unison.

Records of the clinical assessments of the duration of "morning stiffness", of joint swelling and tenderness, and of functional capacity have been omitted, though they are also sensitive indices of changes in adrenocortical activity. When more than one assessment was made each month only the most representative figure was charted. For certain months the steroid assays are missing because the patient "forgot" to collect and bring a 24-hr specimen. During Month 3 (Period A) the corticotropin was given 12-hrly (cross-hatch). During Month 23 (Period B) the response to H.P. Acthar Gel 33307 dropped to nothing. From the 24th month onwards H.P. Acthar Gel P80001 was given (Period C).

(5) A man aged 44 had pituitary hypofunction (due to an inflammatory process) as well as rheumatoid arthritis (Fig. 5, opposite).

Organon's Cortrophin-Z was given, 10 units twice daily (Period A), with an excellent response. Subsequently 20 units were given once daily (Period B), and slowly complete resistance and a severe relapse to an Addisonian state occurred. An immediate response to 10 units daily of H.P. Acthar Gel P80001 followed (Period C).

(6) A woman aged 45 with rheumatoid arthritis developed resistance to an H.P. Acthar Gel preparation and after this Organon's Cortrophin-Z was, for a short time, highly effective. Within 2 weeks resistance developed to Organon's Cortrophin-Z, with local allergic reactions at the sites of injection (Fig. 6, opposite).

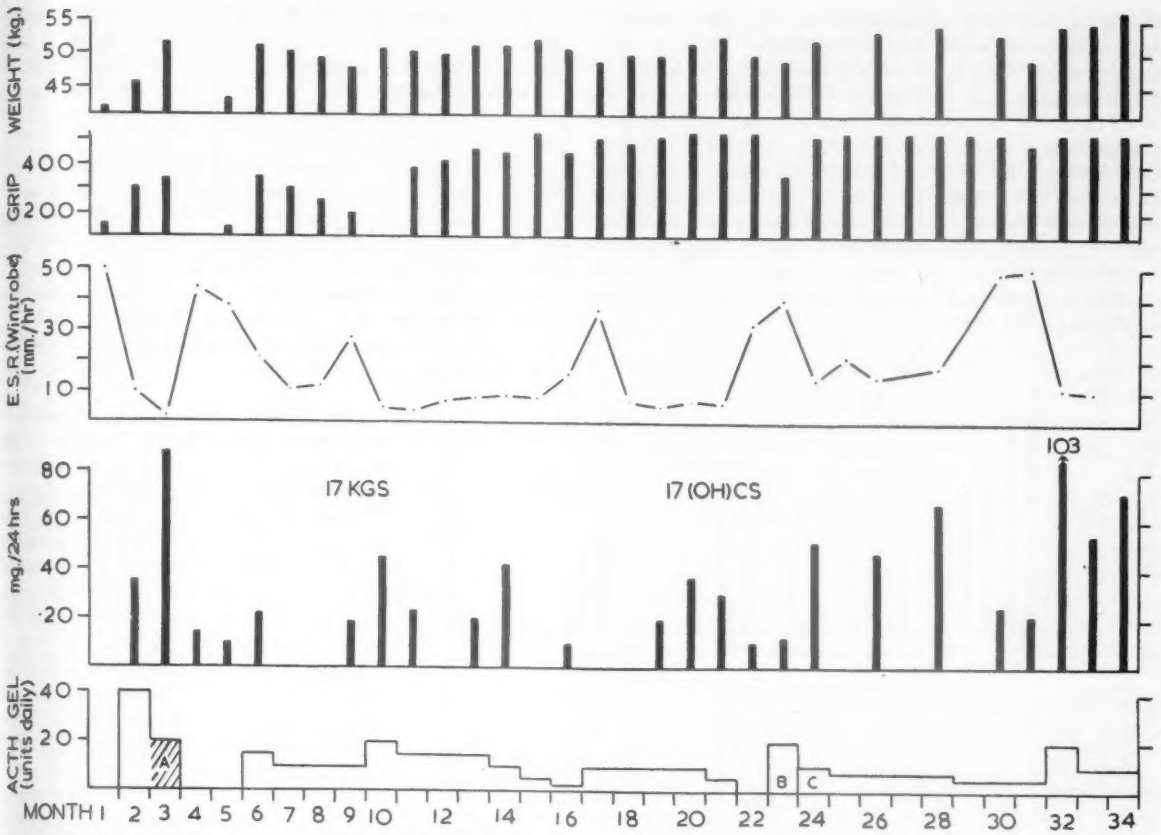


Fig. 4.—Results of 3 years' observations of a young man aged 15 to 18 years with rheumatoid arthritis, showing how different criteria of rheumatoid activity vary in unison.

A—H.P. Acthar Gel 12-hrly (cross hatch), 3rd month.
B—H.P. Acthar Gel (33307), 23rd month.
C—H.P. Acthar Gel (P80001), 24th-34th month.

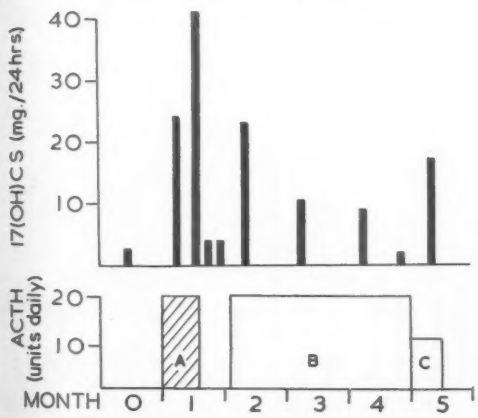


Fig. 5.—Response to Organon's Cortrophin-Z and H.P. Acthar Gel in a man aged 44 with pituitary hypofunction as well as rheumatoid arthritis.

A—Organon's Cortrophin-Z 10 units 12-hrly (cross hatch).
B—Organon's Cortrophin-Z 20 units 24-hrly.
C—H.P. Acthar Gel (P80001) 10 units 24-hrly.

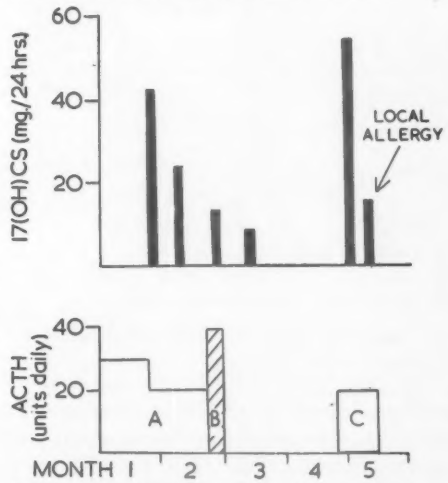


Fig. 6.—Response to H.P. Acthar Gel and Organon's Cortrophin-Z in a woman aged 45 with rheumatoid arthritis.

A—H.P. Acthar Gel 30 and 20 units 24-hrly.
B—H.P. Acthar Gel 20 units 12-hrly (cross hatch).
C—Organon's Cortrophin-Z 20 units 24-hrly.

(7) **A woman aged 50 with rheumatoid arthritis,** showed a loss of response after several months of satisfactory adrenal stimulation (Period A). During Periods B, C, and D, 40 units of H.P. Acthar Gel, Wilson's Gel, and H.P. Acthar Gel 31605 respectively were given in divided

doses 12-hrly—an excessive dose, yet there was no appreciable adrenocortical stimulation. Next an 8-hr intravenous infusion of ACTH was given followed by 6-hrly doses of H.P. Acthar Gel 33307—with no response at all (Fig. 7). A year later a much more highly purified ("improved") experimental preparation of H.P. Acthar Gel AL1033, P7209 was received to which the patient responded immediately (Period F). It may be suggested that during the interval of a year the patient had lost her refractoriness to corticotropin—this is unlikely, since in the 26th month she showed a positive intradermal reaction to 33307 and none to P7209 (both prepared from hog pituitaries).

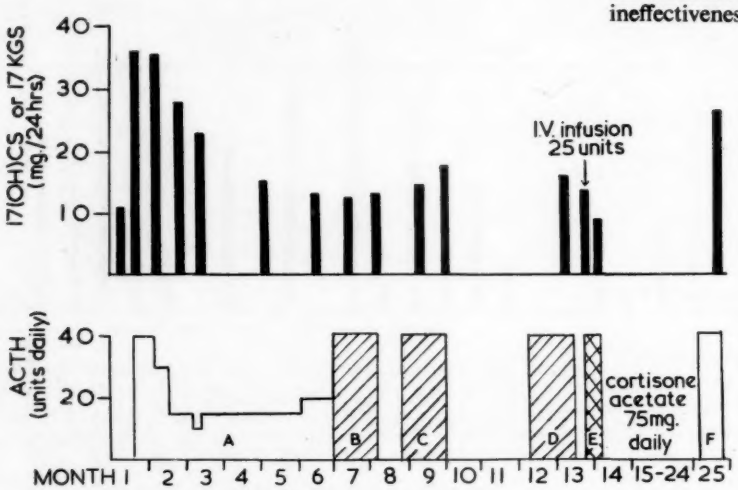


Fig. 7.—Response in a woman aged 50 with rheumatoid arthritis to a series of various preparations of Acthar Gel during a 2-year period of observation.
A—H.P. Acthar Gel 24-hrly.
B—H.P. Acthar Gel 20 units 12-hrly (cross hatch).
C—Wilson's Gel 20 units 12-hrly (cross hatch).
D—H.P. Acthar Gel (31605) 20 units 12-hrly (cross hatch).
E—H.P. Acthar Gel (33307) 10 units 6-hrly (criss-cross).
F—"Improved" H.P. Acthar Gel (AL1033, P7209) 40 units 24-hrly.

(8) A woman aged 37 with rheumatoid arthritis was given Organon's Cortrophin-Z 12-hrly (Period A). On changing to daily injections (Period B) a temporary fall was noted—this is not uncommon when dosage is sharply reduced. The development of resistance was accompanied by local allergic reactions at the site of injection (Fig. 8). During Period C H.P. Acthar Gel P80001 was given, which eventually met with the same fate. The relatively high output in the 8th month, which was in keeping with the clinical state, is not understood.

(9) A woman aged 46 with rheumatoid arthritis responded fairly well for 2 months (Period A) to 30 units daily of an Acthar Gel preparation which had been stored at room temperature for 2 years; she was then given H.P. Acthar Gel 32306 (Period B), and resistance developed (Fig. 9, opposite).

Next Organon's Cortrophin-Z was given in 12-hrly doses, and a poor response was noted which soon failed completely (Period C). The white sections of the columns in the upper part of the chart represent the contribution to the 17(OH)CS of concurrently administered cortisone acetate. The fourth preparation to be given was H.P. Acthar Gel P80001 (Period D); an excellent response was followed by almost complete ineffectiveness within 10 weeks.

(10) A man aged 52 with rheumatoid arthritis was given Acthar Gel during the first month (Period A) with a moderate clinical response (Fig. 10, opposite).

After 18 months of cortisone acetate therapy, Crooke's Zinc protamine ACTH and H.P. Acthar Gel were given with only the slightest response (Period B). Later two 8-hr infusions of ACTH were given followed by 40 units Organon's Cortrophin-Z in divided doses (Period C). On 40 units of the same preparation daily (Period D), the effectiveness soon diminished. It was restored temporarily by giving 12-hrly doses (Period E), but had to be stopped owing to clinical relapse and local allergic reactions at the sites of injection. H.P. Acthar Gel P80001 (Period F) given first daily and then in divided doses produced no response. Duracton (Period G) gave rise to allergic

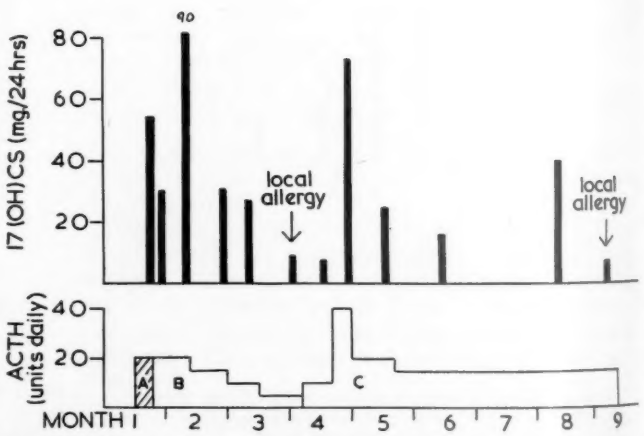


Fig. 8.—Response in a woman aged 37 with rheumatoid arthritis to Organon's Cortrophin-Z and H.P. Acthar Gel, both of which provoked allergic reactions.
A—Organon's Cortrophin-Z 20 units 12-hrly (cross hatch).
B—Organon's Cortrophin-Z in reduced doses 24-hrly.
C—H.P. Acthar Gel (P80001) 24-hrly.

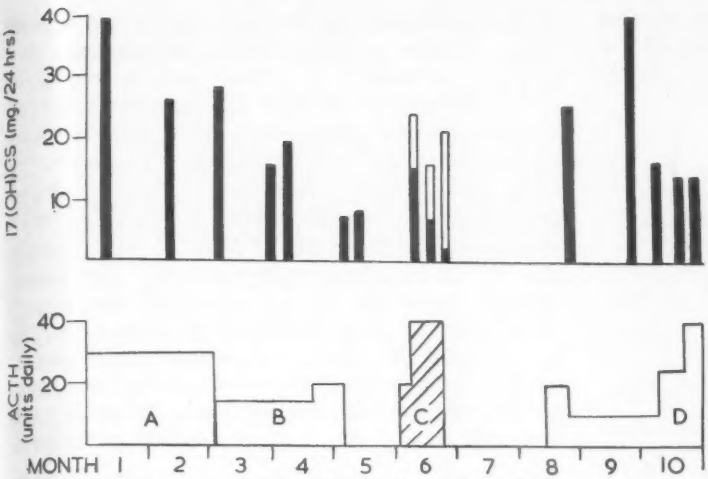


Fig. 9.—Response in a woman aged 46 with rheumatoid arthritis to various preparations of Acthar Gel and Organon's Cortrophin-Z.
A—Acthar Gel which had been stored for 2 years 30 units 24-hrly.
B—H.P. Acthar Gel (32306) 24-hrly.
C—Organon's Cortrophin-Z 12-hrly (cross hatch).
D—H.P. Acthar Gel (P80001) 24-hrly.

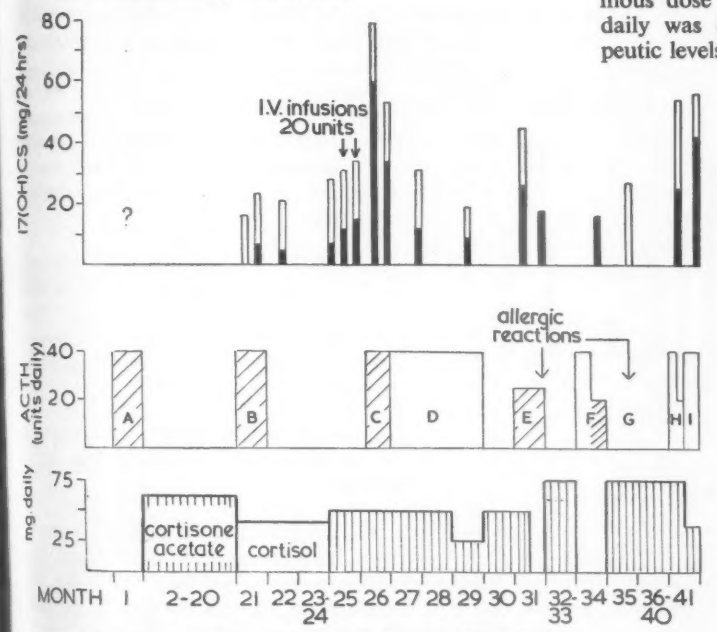


Fig. 10.—Response in a man aged 52 with rheumatoid arthritis to various preparations of Acth, H.P. Acthar Gel, Organon's Cortrophin-Z, Duracton, and Armour's more highly purified gels given in conjunction with cortisone acetate and cortisol.
A—Acthar gel 40 units 12-hrly (cross hatch).
B—Crooke's Zinc protamine Acth and H.P. Acthar Gel 40 units 12-hrly (cross hatch).
C—Organon's Cortrophin-Z 40 units 12-hrly (cross hatch).
D—Organon's Cortrophin-Z 40 units 24-hrly.
E—Organon's Cortrophin-Z 20 units 12-hrly (cross hatch).
F—H.P. Acthar Gel (P80001) 40 units 24-hrly, followed by 20 units 12-hrly (cross hatch).
G—Duracton.
H—Armour's more highly purified beef Acthar Gel 24-hrly.
I—Armour's more highly purified pork Acthar Gel 24-hrly.

reactions immediately. Finally Armour's more highly purified experimental beef and pork Acthar Gels were given with a good response in each case (Periods H and I).

(11) A woman aged 42 with rheumatoid arthritis had had cortisone acetate for 2 years before this observation period began. During Period A Wilson's purified Gel was given and during Period B H.P. Acthar Gel; Wilson's Gel was again given in Period C but in 12-hrly doses, as was H.P. Acthar Gel in Period D. H.P. Acthar Gel P80001 was given in the 18th month (Period E), but was stopped because of ineffectiveness and local reaction at the injection site (Fig. 11, overleaf).

Finally, Duracton was given (Period F), but reaction at the site of injection began immediately. In Period A it will be seen that by the 3rd month of treatment 60 units produced no more stimulation than 20 units produced initially. Only on the enormous dose of 40 units of Wilson's purified Gel twice daily was adrenocortical stimulation raised to therapeutic levels.

This type of response has not been seen after prolonged cortisone acetate therapy in other patients.

Many patients lost their response to H.P. Acthar Gel N31605, and it was suggested that the batch might have been losing its potency through prolonged storage.

(12) A man aged 49 with rheumatoid arthritis, however, continued to respond normally to 31605 (Period A) until the supply of this batch was exhausted (Fig. 12, overleaf).

This example shows how two preparations of equal unit value as judged by biological assay (U.S.P. XV) can prove to be of very different potency in man, since this patient's response to H.P. Acthar Gel P80001 was quite different (Period B).

Allergic Reactions

Local reactions at the site of injection occurred in seventeen patients. The reactions usually appeared after 1 to 2 hours and consisted of an area of induration 3 to 4 cm. across, either subcutaneous or intramuscular, which "burnt" for some hours and slowly disappeared in 6-24 hrs. All the 51 patients received H.P. Acthar Gel for more than a month and six developed local reactions. Of seventeen patients who received Organon's Cortrophin-Z

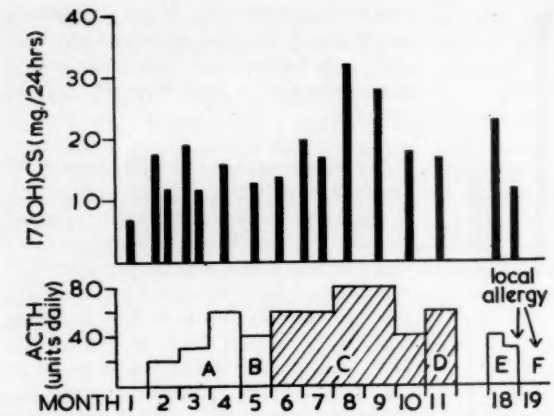


Fig. 11.—Response in a woman aged 42 with rheumatoid arthritis, who had been given cortisone acetate for 2 years before this observation period began, to various preparations of Acthar Gel and Duracton.

A—Wilson's Gel 24-hrly.
B—H.P. Acthar Gel 40 units 24-hrly.
C—Wilson's Gel 12-hrly (cross hatch).
D—H.P. Acthar Gel 60 units 12 hrly (cross hatch).
E—H.P. Acthar Gel (P80001) 24-hrly.
F—Duracton.

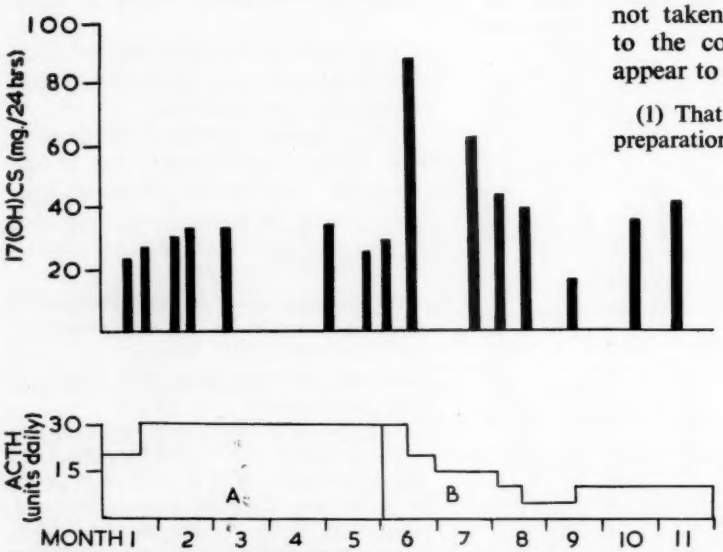


Fig. 12.—Response in a man aged 49 with rheumatoid arthritis to H.P. Acthar Gel 31605 and P80001.

A—H.P. Acthar Gel (31605) 24-hrly.
B—H.P. Acthar Gel (P80001) 24-hrly.

(Batches OA57 and OA61), only nine received it for more than one month, yet ten of the seventeen developed local allergic reactions.

General reactions, apart from anaphylactic shock, were difficult to be sure of in the patients studied, since the appearance of the allergic reactions was always accompanied by a fall in adrenocortical stimulation and a relapse of symptoms. Although no firm evidence can be provided that any of the patients were made ill by receiving allergenic ineffective injections of corticotropin, the impression was gained that in a number of instances this was so. One spondylitic patient had tense knee effusions during ineffective H.P. Acthar Gel therapy which were much easier when the treatment stopped. Another patient became ill and had diarrhoea, while she persisted in giving herself Organon's Cortrophin-Z which was causing local reactions. The patient referred to in Fig. 5, on losing his response to Cortrophin-Z, developed profuse lesions on his hands, legs and feet, resembling those seen in disseminated lupus erythematosus. He died some months later as the result of a pulmonary embolus and the kidney showed lesions of polyarteritis nodosa.

Many patients were tested for intradermal sensitivity to several preparations of corticotropin. The work of Paley (1954) on dermal reactions to insulin has shown that strict precautions and controls are necessary if much is to be deduced from the findings. Although full precautions were not taken in the tests for intradermal sensitivity to the corticotropins, the following observations appear to be justified:

(1) That when resistance was acquired to a particular preparation of corticotropin it was not necessarily accompanied by a positive intradermal reaction.

(2) That a moderate 2 to 3 cm. delayed type reaction to H.P. Acthar Gel did not necessarily mean that the preparation would not be effective when administered in adequate dosage.

(3) That the purer the preparations of corticotropin the fewer the intradermal reactions.

(4) That patients may give a positive intradermal reaction to a pork or beef corticotropin and yet give no reaction to a more highly purified corticotropin from the same species.

Corticotropin A$_1$.—Eleven mg. of this preparation, from pig pituitaries, was made available by Dr. H. B. F. Dixon. One mg. was dissolved in water and used for intradermal testing and the rest was incorporated in Armour's Acthar Gel vehicle for intramuscular injection. Sixteen patients who had previously received corticotropin were tested for skin sensitivity and none gave a positive reaction.

Two of these patients were of particular interest and importance to this study.

(13) A woman aged 40 with rheumatoid arthritis had acquired resistance to several preparations of corticotropin and an attempt to desensitize her with porcine H.P. Acthar Gel had resulted in local allergic reactions of increasing intensity. To the experimental "improved" H.P. Acthar Gels (pork and beef) she gave positive intradermal reactions lasting for 3 days. She was then given 0·2 mg. Corticotropin A_1, 12-hrly for seven doses. Although on a maintenance dose of cortisol (50 mg. daily), her output of 17(OH)CS during the last 24 hrs rose to 92 mg. (a maintenance dose of 50 mg. cortisol indirectly suppresses the adrenal cortex, but does not lessen acquired resistance to administered corticotropin).

(14) A woman aged 27 with rheumatoid arthritis, who did not belong to the long-term corticotropin treatment group, had received cortisone acetate daily for 5 years, and in 1951 she had a short course of corticotropin to re-stimulate her adrenals. When this was attempted again in 1953, with H.P. Acthar Gel, she suffered an alarming anaphylactic reaction. Two and a half years later she gave a positive intradermal reaction to a 1 : 10 dilution of the "improved" H.P. Acthar Gel. Fig. 13 shows her response to Corticotropin A_1. The immediate response of the adrenal cortex and the absence of any allergic reaction was very pleasing.

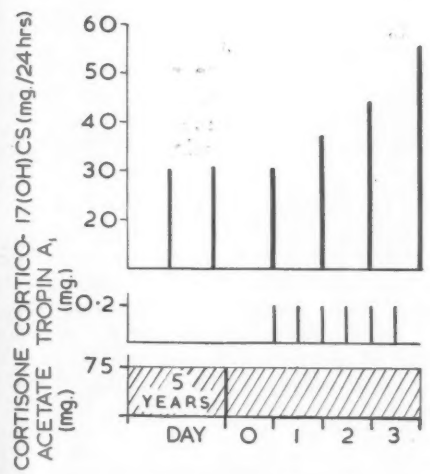


Fig. 13.—Response in a woman aged 27 with rheumatoid arthritis, who had been given cortisone acetate for 5 years, to six injections of Corticotropin A_1 0·2 mg. in 3 days.

(15) A man aged 52 with rheumatoid arthritis, who had had no cortisone to suppress his adrenals, was given Corticotropin A_1, and the response of his adrenal cortex in the first 24 hrs showed that Corticotropin A_1 was far more potent, per mg. protein, than any preparation we had previously used (Fig. 14).

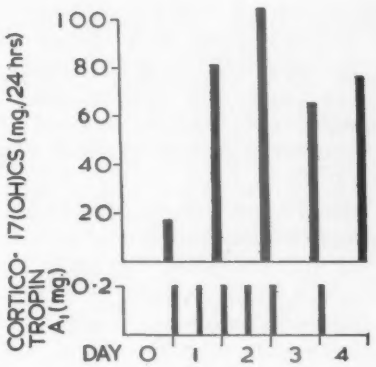


Fig. 14.—Response in a man aged 52 with rheumatoid arthritis, who had had no cortisone, to six injections of Corticotropin A_1 0·2 mg. in 3½ days.

Discussion

There can be no doubt that the loss of effectiveness of "highly purified" corticotropin on prolonged administration is due to the development of an acquired resistance. Exhaustion of the adrenal cortex has been suggested as a possible explanation, but it is clear from the examples given that this is not the case. At this centre we have followed adrenal stimulation therapy through more than 60 patient-years and have never had cause to suspect adrenal exhaustion. The oldest patient (aged 67) appears to have the most responsive adrenal. Loss of effectiveness of corticotropin due to prolonged storage or storage at an unsuitable temperature has also been advanced to explain the falling off of effectiveness. In this study no preparation has at any time been ineffective in a previously untreated patient. The nature of the acquired resistance, however, is not known. Using the early relatively crude corticotropins, several workers have induced and demonstrated circulating antibodies, but similar studies have not been reported with the "highly purified" preparations. It is likely, of course, that cell fixed antibodies are the main cause of the acquired resistance.

Is the pure adrenocorticotropic hormone allergenic in man? Studies of the non-species specific allergic reaction induced by relatively crude corticotropins has led some workers to conclude that the hormone itself must be antigenic (Alexander, 1955). The findings reported here using "highly purified" corticotropins remove the basis on which their

assumption was made. To be certain that it is not allergenic, a pure preparation would have to be administered for prolonged periods to patients who had shown the ability to acquire sensitivity to less pure preparations. It might prove necessary to test the pure hormone from each species used, since although the hog and the ox have the same oxytocin they have different vasopressins (du Vigneaud, Lawler, and Popenoe, 1953). There are also species differences between insulins (Brown, Sanger, and Kitai, 1955).

Nevertheless, the evidence presented above of the specific nature of the acquired resistances and of the response of the two most sensitive patients to Corticotropin A_1 does suggest very strongly that the pure hormone or hormones will not be liable to induce resistance in man. It is possible that Dr. H. B. F. Dixon's Corticotropin A_1 is, in fact, a pure hormone, *i.e.* containing no contaminating protein at all.

The finding of Maddock and others (1956) that non-species specific antigonadotrophins could be induced in man parallels the experience at this centre with the early crude preparations of corticotropin. Solem and Römcke (1954) found that patients who developed allergic reaction to relatively crude whale corticotropin subsequently reacted to a variety of ox pituitary products and to hog corticotropin. They did not, however, have an allergic reaction to H.P. Acthar Gel. Several of the patients referred to in this study had received the early crude corticotropin, but none has been shown to have a non-specific resistance to *all* corticotropins, and it can be seen from the examples given that whenever corticotropin was stopped the endogenous corticotropin was at work. Moloney and Coval (1955), using crystalline insulin with an adjuvant, induced non-species specific anti-insulin sera in guinea-pigs, but the sera did not neutralize the guinea-pigs' own insulin. It may be that there is some other explanation for the finding of Maddock and others that pituitary antigonadotrophin is apparently effective against the patients' own gonadotrophin.

Can allergenic preparations of corticotropin do harm? The crude preparations are clearly dangerous; of the "highly purified" preparations there is some doubt. In this study Organon's Cortrophin-Z (batches OA57 and OA61) were highly unsatisfactory and may have done harm. The H.P. Acthar Gel caused relatively few minor allergic reactions. (Nevertheless, it caused a great deal of inconvenience through the acquired resistance that developed.) It is to be hoped that purer preparations will soon be available.

Summary

Adrenocortical stimulation was maintained for prolonged periods in 51 patients by the intramuscular injection of "highly purified" corticotropin. The level of stimulation, which could be assessed roughly by clinical observation, was measured in all cases by routine urinary corticosteroid assays. During the prolonged therapy, 42 patients acquired resistance to one or more preparations of corticotropin and seventeen patients experienced allergic reactions at the sites of injection. The principal findings are presented and discussed and the following conclusions are thought to be warranted:

(1) That the generally available "highly purified" corticotropin preparations, when given intramuscularly for prolonged periods, are allergenic.

(2) That the allergenic nature of the corticotropins used resided in the contaminating or "carrier" protein that they contained.

(3) That if the pure adrenocortical hormone or hormones prove to be allergenic at all, very few patients will manifest the allergy.

(4) That no evidence has been found to suggest that, when the relatively crude corticotropins are used, anti-corticotropins are formed that are able to destroy the recipient's own corticotropin.

(5) That even the "highly purified" corticotropins in use are not themselves entirely harmless. This may apply especially to patients in a permanent or temporary Addisonian state.

(6) That efforts should be made to obtain more highly purified corticotropin and that preparations of low potency should not be used.

It is recommended that a statement as to *purity*, measured in a recognized unit per mg. protein solid, should accompany all preparations of corticotropin.

Thanks are due to Dr. H. B. F. Dixon of the Department of Biochemistry, University of Cambridge, for the supply of Corticotropin A_1 and to Dr. R. E. Thompson of the Armour Laboratories, Kankakee, for the "improved" experimental H.P. Acthar Gel. Thanks are also due to our laboratory staff for the great care they have taken in performing more than a thousand corticosteroid assays for the patients studied, and to Dr. G. R. Newns for much clinical help.

REFERENCES

Alexander, H. L. (1955). "Reactions with Drug Therapy," p. 136. Saunders, Philadelphia.

Appleby, J. I., Gibson, G., Norymberski, J. K., and Stubbs, R. D. (1955). *Biochem. J.*, **60**, 453.

——, and Norymberski, J. K. (1955). *Ibid.*, **60**, 460.

Brown, H., Sanger, F., and Kitai, R. (1955). *Ibid.*, **60**, 556.

Dixon, H. B. F., and Stack-Dunne, M. P. (1955). *Ibid.*, **61**, 483.

Forsham, P. H. (1955). "Ciba Foundation Colloquia on Endocrinology," **8**, 319. Churchill, London.

Maddock, W. O., Leach, R. B., Tokuyama, I., Paulson, C. A., Nelson, W. O., Jungck, E. C., and Heller, C. G. (1956). "Proceedings of the Fifth International Conference on Planned Parenthood." Tokyo (in the press).

Moloney, P. J., and Coval, M. (1955). *Biochem. J.*, **59**, 179.
Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, 1, 1276.
Paley, R. G. (1954). *Ibid.*, **2**, 1249.
Solem, J. H., and Römcke, O. (1954). *Acta med. scand.*, **149**, 333.
Thompson, R. E., and Fisher, J. D. (1953). *Endocrinology*, **52**, 496.
du Vigneaud, V., Lawler, H. C., and Popenoe, E. A. (1953). *J. Amer. chem. Soc.*, **75**, 4880.
West, H. F., and Newns, G. R. (1955). *Lancet*, **1**, 578.

Résistance acquise aux corticotrophines

RÉSUMÉ

La stimulation surrénocorticale fut maintenue durant des périodes prolongées chez 51 malades par l'injection intramusculaire de corticotrophine "hautement purifiée". Le degré de stimulation, qui pouvait être grossièrement estimé par observation clinique, fut mesuré dans tous les cas par titrage de corticostéroïdes urinaires. Durant le traitement prolongé, 42 malades acquirent une résistance à une ou à plusieurs des préparations de corticotrophine et chez 17 malades des réactions allergiques se produisirent aux points d'injections. Les résultats principaux sont présentés et discutés et les conclusions suivantes semblent être justifiées:

(1) Les préparations "hautement purifiées" de corticotrophine généralement disponibles sont allergènes quand elles sont administrées durant de longues périodes par voie intramusculaire.

(2) La nature allergène des corticotrophines utilisées réside dans la protéine contaminante ou "porteuse" qu'elles contiennent.

(3) En admettant même que l'hormone ou les hormones surrénocorticales pures soient allergènes, cette allergie se manifeste chez peu de malades.

(4) Aucune évidence n'a été trouvé pouvant suggérer que, quand des corticotrophines relativement imparfaites sont utilisées, des anti-corticotrophines se forment, capables de détruire la propre corticotrophine du sujet.

(5) Même les corticotrophines "hautement purifiées" utilisées ne sont pas tout à fait sans danger. Ceci peut s'appliquer spécialement aux malades en état d'addisonisme permanent ou temporaire.

(6) Des efforts doievent être fait en vue d'obtenir de la corticotrophine plus parfaitement purifiée et les préparations faibles ne doivent pas être utilisées.

Il est recommandé qu'une déclaration de *pureté* mesurée en unités souscutanées définies par mg. de protéine solide accompagne toutes les préparations de corticotrophine.

Resistencia adquirida a las corticotrofinas

SUMARIO

Se mantuvo la estimulación adrenocortical durante períodos prolongados en 51 enfermos con inyecciones intramusculares de corticotrofina "altamente purificada". El grado de estimulación, que se podía estimar aproximadamente por observacion clínica, fué medido en todos los casos por métodos habituales de dosificación de corticoesteroides urinarios. Durante el tratamiento prolongado, 42 enfermos adquirieron resistencia a una o más preparaciones de corticotrofina y en 17 enfermos se produjeron reacciones alérgicas en sitios de inyecciones. Se presentan y se discuten los resultados principales, justificando las conclusiones siguientes:

(1) Las preparaciones "altamente purificadas" generalmente disponibles son alérgenas cuando se las administra durantes períodos prolongados por vía intramuscular.

(2) La naturaleza alérgena de las corticotrofinas empleadas se debe a las proteinas contaminantes o "portadoras" contenidas en ellas.

(3) Aunque se pudiera comprobar que la hormona o las hormonas adrenocorticales sean alérgenas, pocos enfermos manifestarían esta alergía.

(4) No se encontraron indicios algunos sugerentes que, al emplear corticotrofinas relativamente imperfectas, se formasen anticorticotrofinas capaces de destrozar las corticotrofinas propias del sujeto.

(5) Hasta las corticotrofinas "altamente purificadas" en empleo presente no son enteramente sin peligro. Esto se aplica en particular a enfermos en estado de addisonismo permanente o temporario.

(6) Esfuerzos se deben hacer para obtener la corticotrofina de mayor pureza y no se deben emplear preparaciones de poca fuerza.

Se recomenda que una declaración de *pureza* medida por unidades subcutáneas definidas por miligramo de proteina sólida acompañe todas las preparaciones de corticotrofina.

Ann. rheum. Dis. (1956), 15, 134.

PILOT STUDY OF INTRA-ARTICULAR PROCAINE AND HYDROCORTISONE ACETATE IN RHEUMATOID ARTHRITIS

BY

G. R. FEARNLEY, RITA LACKNER, R. I. MEANOCK, AND E. G. L. BYWATERS

From the Department of Medicine, Postgraduate Medical School of London

(RECEIVED FOR PUBLICATION MARCH 12, 1956)

For many years the intra-articular injection of procaine, with or without the addition of lactic acid or phosphate, has been advocated in the treatment of both rheumatoid arthritis and degenerative joint disease (osteo-arthritis), but controlled trials have been only rarely conducted. Such results as have been published (Desmarais, 1952) have not indicated any major difference between the solutions used, and it may be that they are in fact all relatively inert. With the introduction of hydrocortisone acetate, clinical and biochemical observations indicated that improvement occurred in a number of patients. Indeed, with cortisone acetate, which seldom produces clinical improvement, statistically significant biochemical improvement, compared with the results of saline injections, was shown to occur in a controlled cross-over trial (Dixon and Bywaters, 1953). It seemed important therefore to assess the practical day-to-day value of hydrocortisone acetate, compared with that of procaine injections for treatment under out-patient conditions, and it was decided to explore the possibilities of a controlled cross-over trial in a small number of co-operative patients. Each patient was to have both treatments and thus to serve as his own control.

Material

Twelve patients with generalized rheumatoid arthritis were selected whose main incapacity could be ascribed to severe involvement of one knee joint. The patient might have a flexion deformity of the severely affected knee, but a range of at least 20° of passive movement was required. The patients had to be co-operative and with a good record of attendance. The erythrocyte sedimentation rate was required to be 20 mm./hr or more (Westergren), indicating some degree of disease activity. The patient was required to be able to walk at least 50 yards with or without a stick.

The patients were allocated at random into two equal groups; of the twelve initially selected, two fell out because of intercurrent illness, and ten therefore completed the trial, five in each group.

Scheme of Trial

One group received a total of four fortnightly injections of 2·0 ml. (100 mg.) hydrocortisone acetate into the affected knee. This was followed by a rest period of 8 weeks after which each patient in this group received a total of four fortnightly injections of 4·0 ml. 2 per cent. procaine into the same joint. They were then observed for a further 8 weeks. In the other group the same procedure was followed, but in the reverse order.

Fig. 1 (opposite) shows the design of the trial, and the mean erythrocyte sedimentation rate at each attendance of the two groups for the whole period of 28 weeks. The following simple measurements were made initially and at each fortnightly attendance throughout the trial:

Erythrocyte sedimentation rate (Westergren),
walking time (time taken to walk 50 yards),
range of movement of knee (judged by eye),
limitation of knee extension (judged by eye),
joint tenderness at the knee (0—no tenderness; 1—patient states joint is tender; 2—patient winces; 3—withdrawal and/or exclamation).

In addition, an assessment was made of functional status in five grades, and joint circumference, quadriceps circumference, and the volume of fluid aspirated were measured on each occasion, but as these criteria showed no important changes they are not included in the reported results.

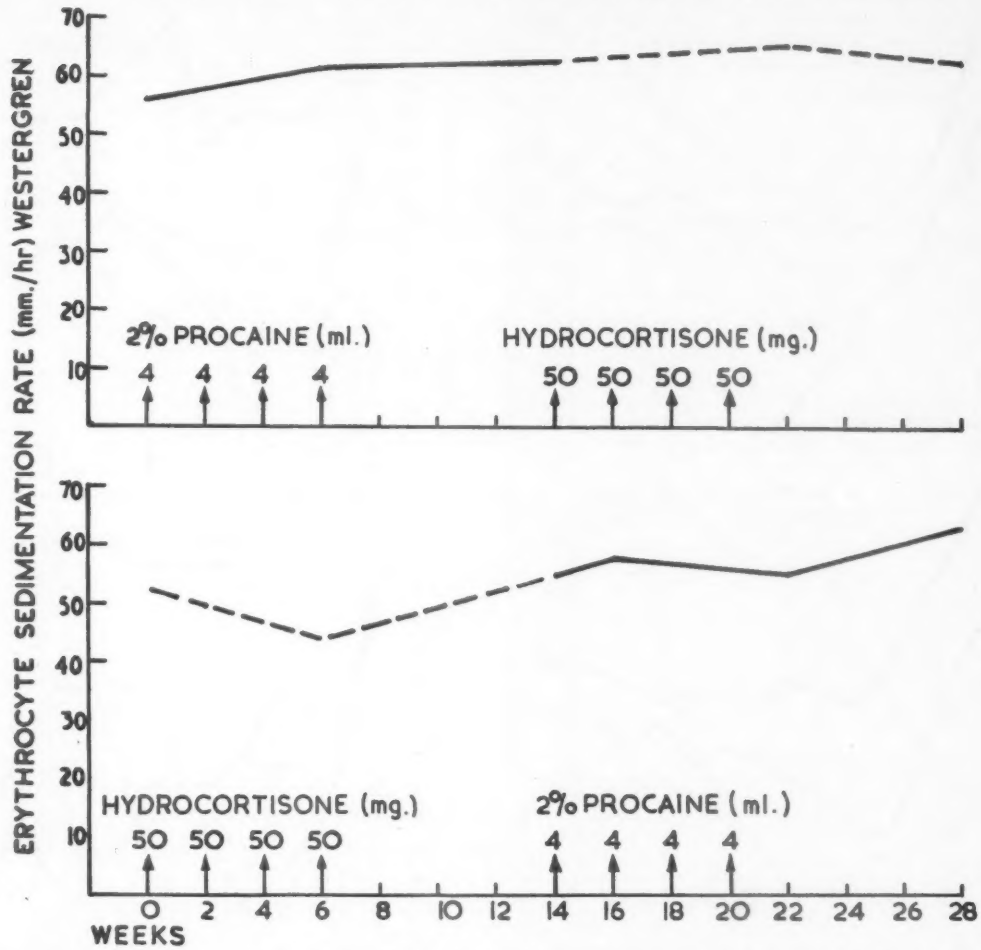


Fig. 1.—Design of trial and mean erythrocyte sedimentation rate of each group during the whole 28 weeks (five patients in each group).

Results

The mean measurements at fortnightly intervals for each group are shown in Figs 2 to 5 (overleaf).

Walking Time.—The mean of each group (Fig. 2) shortened during the first course of injections in all patients of both treatment groups. Little change occurred in either group during the rest period (6-14 weeks). In the group receiving hydrocortisone first, the walking time increased somewhat at the end of the first rest period, and this increase, marked in two patients, continued throughout the procaine injections and the second rest period. In contrast, the group receiving procaine first, showed no relapse during hydrocortisone injections or during the subsequent rest period.

Range of Movement.—The changes showed a somewhat similar pattern to that of the walking time (Fig. 3). Both groups showed an increase in range during the first course of injections, whether of procaine or hydrocortisone. The group receiving hydrocortisone first relapsed during the rest period, levelled off somewhat during the procaine injections, and relapsed again during the second rest period. The group receiving procaine first maintained their improvement throughout the remainder of the trial.

Limitation of Extension.—The mean of the two groups is shown in Fig. 4. In the group receiving hydrocortisone first, there was a marked reduction of limitation, followed by a relapse in the first rest period, some further improvement during the procaine injections, and a further relapse during the second rest period. The other group showed slight improvement with procaine, a relapse during the rest period, and moderate improvement with hydrocortisone. It may be that the amount of

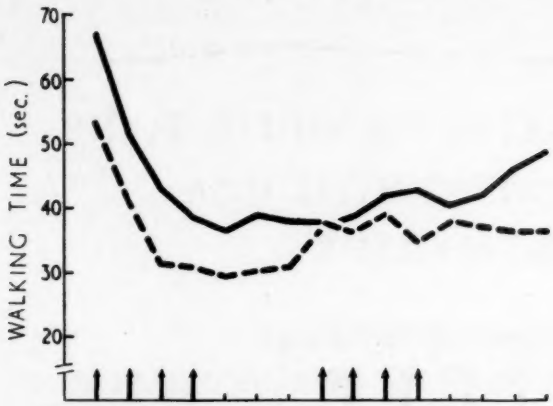


Fig. 2.—Mean walking time in each group during 28 weeks.

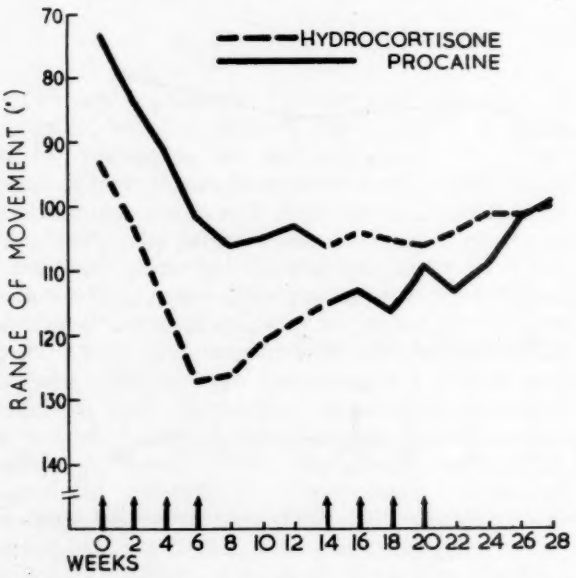


Fig. 3.—Mean range of movement in each group during 28 weeks.

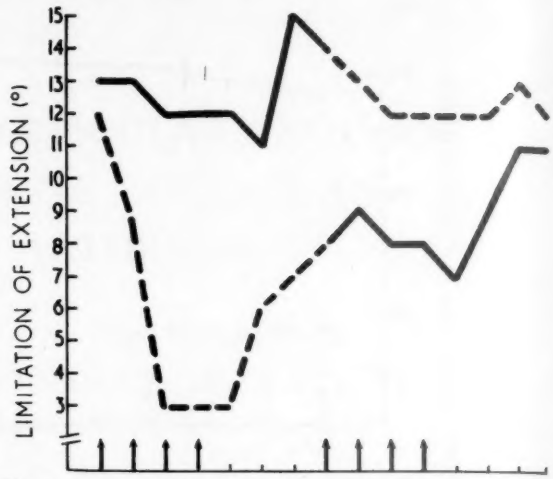


Fig. 4.—Mean limitation of extension in each group during 28 weeks.

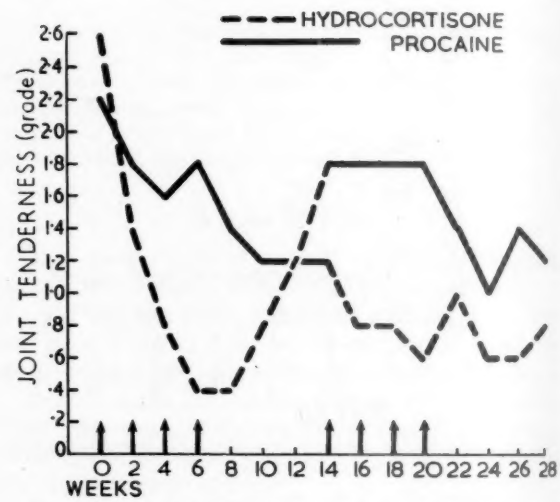


Fig. 5.—Mean joint tenderness in each group during 28 weeks.

possible improvement differed between these two groups.

Joint Tenderness (Fig. 5).—This decreased sharply in the group receiving hydrocortisone, and at first disappeared completely in four out of five. This was followed by a relapse during the first rest period, a levelling off during procaine injections, and a further improvement following the procaine. The group receiving procaine first showed a more moderate improvement which continued during the first rest period and during the hydrocortisone injections.

Combined Measurements.—Fig. 6 (opposite) shows the data in terms of the injections irrespective of group, and illustrates the mean measurements of all patients during the procaine injections, the hydrocortisone injections, and the subsequent rest period. When the results are expressed in this way, it is seen that walking time and range of movement showed comparable improvement with procaine and with hydrocortisone. Limitation of extension was improved by hydrocortisone, but only slightly by procaine, with a relapse during the rest period. Joint tenderness decreased on hydrocortisone and increased again afterwards; there was no response to procaine, but improvement occurred during the rest period after the procaine injections.

The groups are somewhat small for statistical comparisons, and the range of variation from patient to patient is large. Thus, if comparison is made between the change in each individual during the hydrocortisone injections (Week 0 data minus Week 8 data, and Week 14 data minus Week 22

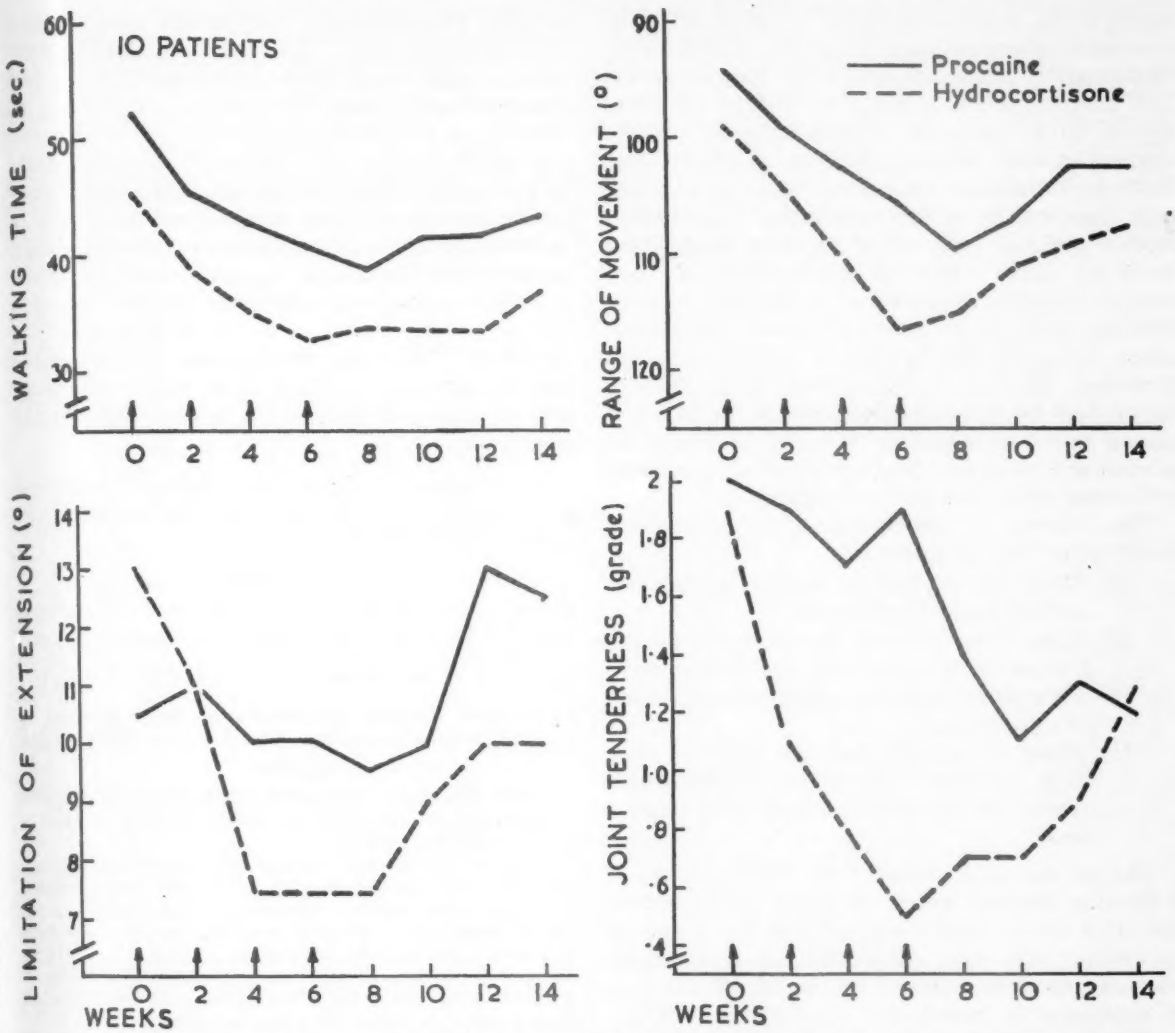


Fig. 6.—Comparison of average measurements of all patients combined during the two injection periods and subsequent rest periods.

data) and during the procaine injections, the difference between the average changes for the two drugs in no instance exceeds twice the standard error of that difference and hence is not significant. The criterion which came nearest to significance (a ratio of 1·84) was "limitation of extension". The difference between the two drug groups in the first 8 weeks only, *i.e.* considering only the first treatment, does not reach levels of significance.

For overall comparison, a weighted score was made for each patient giving approximately equal weight to all the criteria used. This arbitrary score ranged between 219 and 24 points for this group of ten patients. Changes occurring during this first treatment (*i.e.* in the first 8 weeks) show significant improvement over those occurring during the second treatment (between Weeks 14 and 22), irrespective of the drug used; this gives a difference between the means which is 5·6 times the standard error of the difference. There is no difference between the drugs if they are analysed in the same way. There was only a very slight correlation between the scores achieved by individual patients in the first treatment and those achieved in the second. Thus, if the patients are ranged in ranking order according to their score in the first treatment, and comparison is made with their score in the second, "tau", which should be +1 for complete agreement and −1 for complete disagreement, comes out at 0·25.

Discussion

This trial was planned to explore the possibilities of a cross-over design, and not primarily designed to

evaluate the substances used. Despite the small number of observations, some trends of interest for the design of more definitive trials may be noted. The spacing, amount, and duration of injections seemed to be adequate to produce quite marked changes in some criteria. It must be remembered that the fortnightly assessment was made before each injection, by which time any analgesic effect from a previous injection of procaine would have worn off. The length of time between the two courses of injections seemed to be adequate to show reversion towards the untreated state. The importance of a preliminary period of training as noted previously (Bywaters, Dixon, and Wild, 1950) is shown here by this difference between the first and second period of injections; it would have been an advantage here to have had a preliminary treatment with some other therapeutic substance.

The criteria of assessment group themselves chiefly into three categories:

(1) Those that showed no regular change and are not further considered;
(2) Those that showed improvement in the first period of either drug, and little or none in the second period (walking time and range of movement);
(3) Those that showed the same trend for each drug, in both the first and second course (limitation of extension and joint tenderness).

The last are to be preferred for the evaluation of differences between drugs. It seems probable that the other two criteria (walking time and range of movement) are more susceptible to non-specific encouragement, and depend on the patient's degree of confidence in himself and his physician. Thus, of the nine criteria used, only two appeared from this pilot study to be of potential value. It is important to define the value of these criteria, since one of the reasons why controlled clinical trials are not performed is the fact that assessment is time-consuming and often tedious, even though, as in this instance, the patients are carefully selected and co-operative, and the examining physicians personally interested in the results of the trial.

Summary

The effects of intra-articular injections of hydrocortisone acetate and of procaine was studied in ten patients, as a pilot scheme.

Each patient was given four fortnightly injections of one drug followed by 8 weeks' rest, and four fortnightly injections of the other drug followed by a further 8 weeks' rest. Five patients chosen at random received hydrocortisone first and five others received procaine first. Assessment was made at fortnightly intervals. The only significant difference was that found between the results of the first treatment and those of the second, regardless of which drug was used.

It was found that the criteria of assessment could be grouped into three categories: those that showed no regular change, those that showed improvement in the first course but not the second, and two (joint tenderness and limitation of extension) which showed a similar change for each drug whether the drug was given in the first or in the second course of injections. On these two criteria hydrocortisone acetate appeared to show some slight advantage over procaine, although this was not statistically significant.

We are grateful to Dr. E. Lewis-Faning for his helpful criticism, and to the Empire Rheumatism Council for a supply of hydrocortisone.

REFERENCES

Bywaters, E. G. L., Dixon, A. St. J., and Wild, J. B. (1950). *Lancet*, 1, 951.

Desmarais, M. H. L. (1952). *Annals of the Rheumatic Diseases*, 11, 277.

Dixon, A. St. J., and Bywaters, E. G. L. (1953). *Clin. Sci.*, 12, 15.

Étude-pilote d'emploi intra-articulaire de la procaïne et de l'acétate d'hydrocortisone dans l'arthrite rhumatismale

RÉSUMÉ

L'effet d'injections intra-articulaires d'acétate d'hydrocortisone et de procaine fut étudié sur dix malades à titre d'expérience-pilote.

Chaque malade reçut quatre injections bi-hebdomadaires de l'une des substances, suivies par huit semaines de repos, puis quatre injections bi-hebdomadaires de l'autre substance, suivies à nouveau de huit semaines de repos. Cinq malades, choisis au hazard, furent traités d'abord à l'hydrocortisone, et cinq autres furent traités d'abord à la procaine. L'évaluation des résultats fut faite à des intervalles bi-hebdomadaires.

La seule différence significative, fut celle observée entre les résultats du premier traitement et ceux du second, quelle que fût la substance employée.

On trouva que les critères d'évaluation des résultats pouvaient être rangés en trois catégories: ceux qui ne montraient aucun changement constant, ceux qui accusaient une amélioration dans la première partie du traitement mais non dans la seconde et ceux, comprenant la sensibilité articulaire el la limitation de l'extension, qui accusaient un changement similaire pour chaque substance, que celle-ci fût administrée durant la première ou la seconde série d'injections. Selon ces deux critères, l'acétate d'hydrocortisone sembla montrer un léger avantage sur la procaine; cet avantage ne fut pas significatif du point de vue statistique.

Estudio-piloto del empleo intra-articular de la procaina y del acetato de hidrocortisona en la artritis reumatoide

SUMARIO

El efecto de inyecciones intra-articulares de acetato de hidrocortisona y de procaina fué estudiado en diez enfermos a título de estudio-piloto.

Cada enfermo recibió cuatro inyecciones quincenales

de un producto, seguidas de ocho semanas de resposo, luego cuatro inyecciones quincenales del otro producto, también seguidas de ocho semana de reposo. Cinco enfermos escogidos al azar empezaron con inyecciones de hidrocortisona y los cinco demás con las de procaina. Cada quincena se avaluaron los resultados.

La única diferencia significativa fué la observada entre los resultados del primer tratamiento y los del segundo, cualquier fuera el producto empleado.

Los criterios de avaluación se podían agrupar en tres categorías: los que no presentaron cambios constantes, los que acusaron una mejoría en la primera parte del tratamiento pero no en la segunda y, finalmente, los que mostraron una tendencia similar para ambos productos en ambas series de inyecciones. En este tercer grupo se encuentran la sensibilidad articular y la limitación de la extensión. Estos dos criterios sólo se pueden tomar en cuenta y según ellos el acetato de hidrocortisona parece tener una pequeña ventaja, sin importancia estadística, sobre la procaina.

Ann. rheum. Dis. (1956), **15**, 140.

UVEITIS AND RHEUMATIC DISEASES

BY

A. STANWORTH AND J. SHARP

Departments of Ophthalmology and Rheumatology, University of Manchester

(RECEIVED FOR PUBLICATION FEBRUARY 17, 1956)

Historical Survey

Many isolated examples of the association of uveitis and rheumatic diseases occur in the literature, but there have been few attempts to assess the extent of this association.

Rheumatic Diseases in Uveitis.—Some of the series of patients with uveitis in whom the incidence of rheumatic diseases has been investigated are shown in Table I. The reported incidence of spondylitis varies from 2·4 to 25·6 per cent., and it is probably significant that Vesterdal (1951) found that the incidence increased from 5·7 to 20 per cent. when routine radiographs of the sacro-iliac joints and spine were taken. Iritis has been reported as the initial manifestation of ankylosing spondylitis by Teschendorf (1933), Birkbeck, Buckler, Mason, and Tegner (1951), Forestier (quoted by Romanus, 1953), and Romanus (1953).

Vesterdal (1951), who found rheumatoid arthritis

TABLE I

INCIDENCE OF RHEUMATIC DISEASE IN PATIENTS WITH UVEITIS

Author	Date	Type of Investigation for Rheumatic Diseases	Type of Uveitis	No. of Patients	Rheumatic Diseases Found		
					Disease	No.	Per cent.
Schley	1937	Clinical, with radiographs of great majority	Diffuse superficial iritis	73	Ankylosing spondylitis Spondylosis deformans	10 40	13·7 55
			Focal uveitis	32	Spine normal	All	
Guyton and Woods	1941	No special examination	All types	562 in-patients (1925-39)	"Infectious arthritis" Acute rheumatic fever	8 3	1·4 0·5
Berens, Rothbard and Angevine	1942	Not stated	Acute or chronic uveitis	63	Rheumatoid arthritis	2	3·2
Müller	1949	Not stated	Endogenous non-purulent uveitis	861	Chronic rheumatism Von Bechterew's disease	137 21	15·9 2·4
Vesterdal	1951	Clinical, radiology not routine	Acute fibrinous iridocyclitis	70	Ankylosing spondylitis	4	5·7
		Clinical with routine radiology	Acute fibrinous iridocyclitis	50	Ankylosing spondylitis	10	20
		Total	Acute fibrinous iridocyclitis	120	Chronic rheumatoid arthritis Acute rheumatoid arthritis Gonorrhoea	19 5 23	15·8 4·2 19·2 (Of these at least sixteen had arthritis)
Schöne and Steen	1951	Routine radiographs of sacro-iliac joints	Sample of patients with acute iridocyclitis of doubtful aetiology	105	Definite or doubtful ankylosing spondylitis	7	6·7
Bartoš	1952	Not known	Not known	78	Definite Bechterew's disease Possible Bechterew's disease	20 6	25·6 7·7
De Marchin	1954	Routine radiographs of sacro-iliac joints	Ocular inflammation, suspected of rheumatic origin.	80	Bilateral sacro-iliac arthritis (Of these, seven (8·7 per cent.) had spinal changes of ankylosing spondylitis)	15	18·7
Bennett	1955	Not stated	"Primary uveitis"	332	Ankylosing spondylitis Rheumatoid arthritis Previous rheumatic fever	34 27 5	10·2 8·1 1·5

in 20 per cent. of her patients, is the only author to report any striking association of rheumatoid arthritis with uveitis.

A diagnosis of "Reiter's disease" was not made in any of the above studies, but Vesterdal found clinical or serological evidence of "gonorrhoea" in 23 (19·2 per cent.) of her patients, and sixteen of them (69·4 per cent.) had arthritis.

Uveitis in Rheumatic Diseases.—The reported incidence in rheumatic diseases has varied widely. In the larger reported series of cases of ankylosing spondylitis, uveitis was noted in less than 10 per cent. of cases by Fischer and Vontz (1932), Golding (1936), Scott (1942), Polley and Slocumb (1947), Parr, White, and Shipton (1951), Sharp and Easson (1954), and Michaud and Forestier (1954). Hench, Slocumb, and Polley (1947) found an incidence of 11·6 per cent., Hart (1955) 13·5 per cent., West (1949) 15 per cent., Bernstein and Broch (1949) 20 per cent., and Romanus (1953) 28 per cent. Hart (1951) found that the incidence in patients over 45 years of age whose disease was of 15 or more years duration rose to slightly more than 40 per cent.

Conjunctivitis is the commonest reported ocular manifestation of Reiter's disease, but Paronen (1948) found iritis in 21 (6·6 per cent.) of his 334 patients, and Zewi (1947) in one of his ten patients. Ford (1953) found relapsing iritis in six of 21 patients, selected as having recurrent or chronic arthritis over a period of 5 years or more, associated with venereal urethritis.

The highest reported incidence of uveitis in rheumatoid arthritis (4·7 per cent.) is that of Bauer (quoted by Berens, Rothbard, and Angevine, 1942); Duthie (1955) found that seven out of 210 patients with rheumatoid arthritis showed signs of active or old uveitis; Michaud and Forestier (1954) did not encounter uveitis in a study of 100 rheumatoid patients.

It is generally agreed that uveitis is rare in acute rheumatism (Coburn, 1931; Rudolph, 1945; Sorsby and Gormaz, 1946; Nutt, 1951). Godtfredsen (1949), however, reported iritis in 4 to 5 per cent. of patients with rheumatic fever in Denmark, but the basis for this statement was not made clear.

Material and Methods

This study forms part of a wider survey of the aetiological factors concerned in uveitis conducted by one of us (A.S.). The material comprised all patients attending the Out-patient Clinic of the University Department of Ophthalmology between January, 1953, and June, 1955, suffering from uveitis, excluding those with frankly purulent infections (panophthalmitis), post-operative uveitis, and kerato-uveitis in which the uveitis was relatively mild and apparently dependent on the accompanying keratitis (*e.g.* uveitis associated with septic corneal ulcers). Those with kerato-uveitis in which the uveitis formed a major part of the disease picture, and appeared to progress independently of the keratitis, were included in the series. No patients had been referred directly from the Rheumatism Centre to the Eye Department.

The patients were routinely referred to the Rheumatism Centre, where a complete clinical examination of the limbs and spine was performed; almost all the patients were examined by one of two observers who were unaware of the exact type of uveitis present. Radiographs of the limbs and spine were done only when considered indicated on clinical grounds. The sheep cell differential agglutination test for rheumatoid arthritis (D.A.T.) was carried out by Dr. J. Ball (Ball, 1950); agglutination at a dilution of 1/32 or more at 18 hrs was taken as a positive result.

Definition of Terms

Types of Uveitis.—The ocular disease diagnosed at the patient's first attendance was classified as kerato-uveitis, anterior uveitis (iritis or cyclitis, alone or together), posterior uveitis (choroiditis with or without cyclitis), or pan-uveitis (iritis, cyclitis, and choroiditis). The anterior uveitis group was further sub-divided into three types:

(*i*) *Granulomatous.*—This type is characterized by an insidious onset and chronic course, organic changes in the iris, a tendency to form posterior synechiae, and keratic precipitates (K.P.) on the back of the cornea which vary in size but may be "mutton fat" in type.

(*ii*) *Non-granulomatous.*—This type has an acute onset and relatively short duration, the iris shows oedema without gross organic changes, there is copious exudate into the anterior chamber, but the exudate is easily absorbed and posterior synechiae are not marked except after recurrent attacks, and K.P. are small; individual attacks have a relatively good prognosis, but the uveitis tends to recur and may then lead to permanent loss of vision.

(*iii*) There remained a number of cases in which the classification was in doubt.

The patients were also classified into those with and those without a known non-rheumatic cause for the uveitis. Such a subdivision would probably be made in different ways by different ophthalmologists; in the present state of our ignorance only well-substantiated causes can be accepted. We have taken uveitis to be of non-rheumatic origin when associated with herpes zoster ophthalmicus, dendritic ulceration of the cornea, interstitial keratitis, secondary syphilis, superficial punctate keratitis, sarcoidosis, sympathetic ophthalmia, rupture of the lens, heterochromic cyclitis, and Vogt-Koyanagi syndrome.

Types of Rheumatic Disease.—The main classifications of rheumatic disease employed were osteo-arthritis, rheumatoid arthritis, "Reiter's disease", and "spinal

arthritis". The category of osteo-arthritis was further subdivided into degenerative joint disease and "generalized" osteo-arthritis as described by Kellgren and Moore (1952); "spinal arthritis" was subdivided into ankylosing spondylitis and "atypical" spondylitis. The remaining rheumatic diseases, using the term in a broad sense, were grouped together as "other diseases".

Degenerative joint disease was diagnosed when the joint changes appeared to be due to wear and tear. Usually only a few joints such as the larger weight-bearing joints in the elderly were affected. In younger patients the changes had usually occurred in joints which were mechanically deranged or had been subjected to excessive stress. Evidence of degeneration of intervertebral disks was regarded as the analogous process in the spine.

The criteria for the diagnosis of "generalized" osteo-arthritis was a polyarthritis most commonly affecting the interphalangeal joints of the fingers, first carpo-metacarpal, knee, first metatarsophalangeal, and spinal apophyseal joints; this was usually associated with Heberden's nodes and characterized by painful and usually self-limiting episodes in the affected joints with coincident development of bony enlargement of the joints but without peri-articular soft tissue swelling or other associated features of rheumatoid arthritis.

Rheumatoid arthritis was defined as an arthritis, apparently unrelated to infection, showing a strong tendency to symmetrical involvement of distal joints of the extremities with thickening of peri-articular soft tissues of affected joints, a variable degree of constitutional upset, a tendency to formation of nodules in tendons and less frequently in subcutaneous tissues, and usually associated with vasospasm and excess sweating of the extremities and atrophy of the skin and wasting of muscles. Radiographic signs of juxta-articular porosis or articular erosions, and a positive sheep cell differential agglutination test, were considered strong evidence of rheumatoid arthritis, but were not essential for the diagnosis.

The term "Reiter's disease" was used to designate a syndrome characterized by conjunctivitis or uveitis and arthritis with a characteristic distribution and evolution following genito-urinary infection, usually urethritis (Harkness, 1950; Ford, 1953) or following dysentery (Reiter, 1916; Fiessinger and Leroy, 1916; Paronen, 1948; Marche, 1951). In the female, severe or recurrent cystitis or a persistent vaginal discharge was accepted as the genito-urinary component. Stomatitis might occur as a less constant feature of the syndrome (Piora, 1953). In a few instances, as described in the text, Reiter's disease was diagnosed in the absence of definite arthritis, but a history of dysentery or genito-urinary infection was considered essential.

Criteria for the diagnosis of ankylosing spondylitis were based on the clinical descriptions in numerous recent publications (Polley and Slocumb, 1947; Mowbray, Latner, and Middlemiss, 1949; Hart, Robinson, Allchin, and Maclagan, 1949; Hart, 1955). A history of upward spread of the spinal involvement and of exacerbation of symptoms following immobility was almost invariably obtained and movements of the lower spine and chest expansion were usually but not invariably restricted. Bilateral radiographic sacro-iliac joint changes were considered essential for definite diagnosis.

"Atypical" spondylitis was diagnosed in patients with spinal arthritis in whom the clinical or radiographic picture differed in various ways from that of classical ankylosing spondylitis, as described in the text.

In a few patients it was not possible to make a definite differential diagnosis between Reiter's disease, rheumatoid arthritis, and ankylosing spondylitis. In some cases, osteo-arthritis coexisted with one of those conditions. If rheumatoid arthritis entered into the differential diagnosis, this was considered the "main rheumatic disease" (see Table III); similarly, Reiter's disease was given preference over ankylosing spondylitis and each of those three conditions was listed as the main diagnosis in preference to osteo-arthritis.

Results

Table II shows the numbers of patients suffering from the various types of uveitis, subdivided into those with and those without a known non-rheumatic aetiology. Table III (opposite) shows the numbers of patients with rheumatic diseases; the corresponding age distributions are depicted in the Figure (opposite).

TABLE II
TYPE OF UVEITIS

Origin of Uveitis		Kerato-Uveitis	Anterior Uveitis			Posterior Uveitis	Pan-Uveitis	Total
			Granulo-matous	Non-granu-lomatous	Doubt-ful			
Unknown	Male	6	10	55	17	9	2	99
	Female	8	33	31	10	20	1	103
	Total	14	43	86	27	29	3	202
Non-rheumatic	Male	10	4	3	1	0	0	18
	Female	11	4	1	1	0	0	17
	Total	21	8	4	2	0	0	35
Total		35	51	90	29	29	3	237

TABLE III
TYPE OF MAIN RHEUMATIC DISEASE

Type of Uveitis ..	Kerato-Uveitis		Anterior Uveitis						Posterior Uveitis		Pan-Uveitis		Total	
			Granulo-matous		Non-granulo-matous		Doubt-ful							
Origin of Uveitis ..	U.	Non-R.	U.	Non-R.	U.	Non-R.	U.	Non-R.	U.	Non-R.	U.	Non-R.	U.	Non-R.
Total examined for rheumatic disease ..	13	17	38	6	83	1	21	1	26	0	3	0	184	25
Total found to have rheumatic diseases ..	11	11	26	4	60	0	16	0	10	0	2	0	125	15
Osteo-arthritis and degenerative disease	5	4	11	2	11	0	5	0	5	0	1	0	38	6
Rheumatoid arthritis ..	2	2	6	0	9	0	2	0	1	0	0	0	20	2
Reiter's disease ..	2	2	2	0	6	0	3	0	1	0	0	0	14	2
Spinal arthritis ..	2	1	0	0	29	0	6	0	0	0	1	0	38	1
Other rheumatic diseases	0	2	7	2	5	0	0	0	3	0	0	0	15	4

U. = uveitis of unknown aetiology. Non-R. = uveitis of non-rheumatic aetiology.

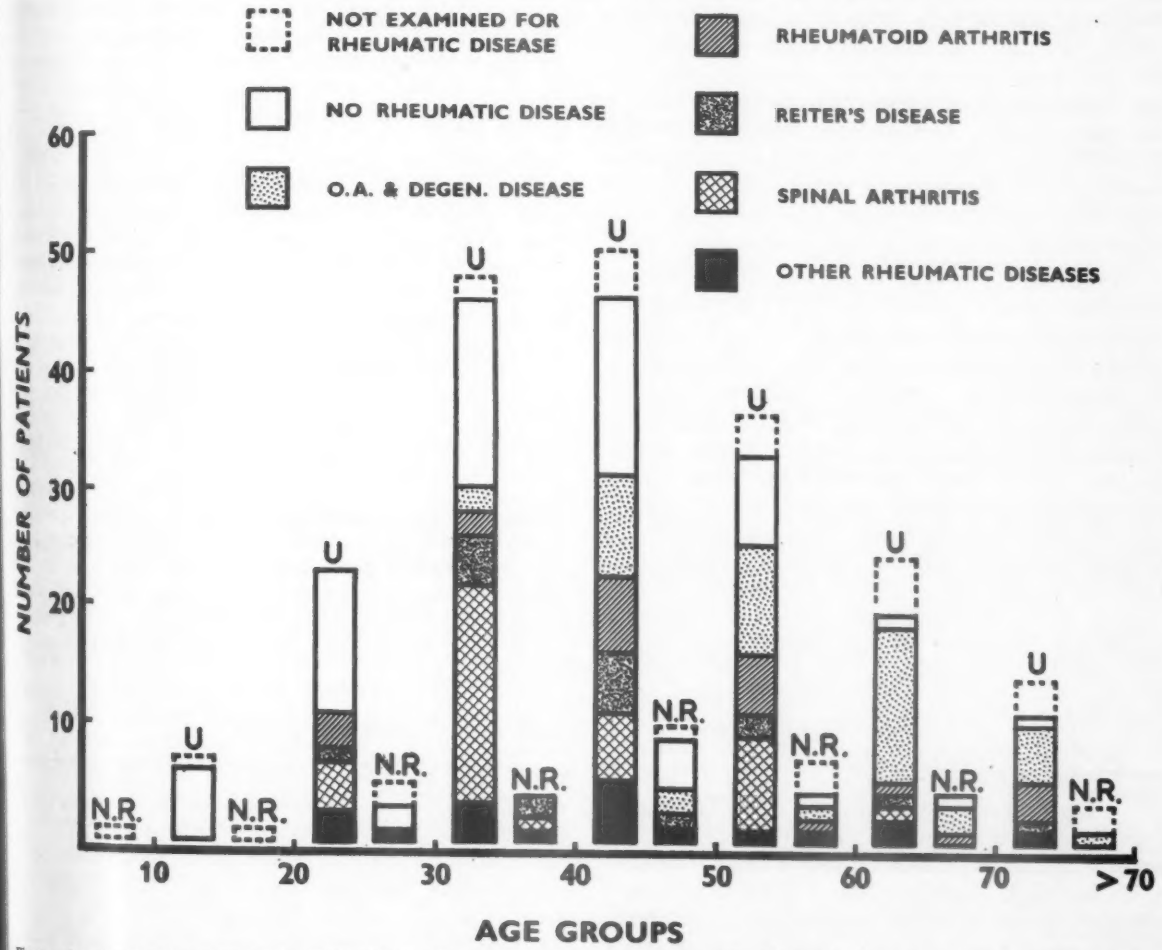


Figure.—Age distribution of patients. Each pair of columns represents one age group. The left-hand column in each pair refers to patients without a known non-rheumatic cause for uveitis (U=unknown) and the right-hand column to those with a known non-rheumatic cause. N.R.=non-rheumatic).

The proportion of patients who failed to attend for rheumatological examination increased steadily after the fourth decade, but otherwise the patients examined formed a reasonably representative sample of the total.

OSTEO-ARTHRITIS.—This was the main diagnosis in 44 patients; in addition, two patients with rheumatoid arthritis and one with spondylitis also suffered from osteo-arthritis; 28 of these 47 patients had generalized osteo-arthritis. Table IV shows that there was no significant difference in the incidence of these diseases in patients with and in patients without a known non-rheumatic cause for their uveitis, and further analysis of the incidence in these groups by age and sex failed to reveal any significant differences.

It is possible to compare the incidence, in this series, of generalized osteo-arthritis in the age group 55-64 years with that in the general population of the South Lancashire town of Leigh (Lawrence, 1955). In the Leigh survey, approximately half the females and one in seven of the males had some clinical evidence of generalized osteo-arthritis; in the present series, this condition was found in eight of the twelve females and none of the thirteen males examined for rheumatic diseases. There was no significant difference between the incidence in the Leigh survey and in the present series.

RHEUMATOID ARTHRITIS.—Eight of the 22 patients with rheumatoid arthritis had clinical evidence of rheumatoid arthritis with bony erosions in radiographs of the hands and feet, three of these having a positive D.A.T. Strong clinical evidence was present in three cases, radiographs and D.A.T. not having been done in one case, and being negative in two cases. Seven patients had some clinical evidence of rheumatoid arthritis but a negative D.A.T. and, in two cases, negative radiographs. One patient had no clinical evidence of disease of the limbs or spine, but his D.A.T. titre was 1/32, 1/64, and $<1/4$ at intervals over $2\frac{1}{2}$ years. The three remaining patients whose case histories are outlined below gave positive results in the D.A.T., but the clinical picture was not that of straightforward rheumatoid arthritis, and these patients were also included in the group with "atypical" spondylitis discussed later.

Case 1, a man aged 21 years, with left non-granulomatous anterior uveitis, gave a history of recurrent inflammation of the eye since the age of 13 years and of a prolonged episode of arthritis in one knee starting at 14 years, subsiding in 2 years without residua apart from alteration of bone architecture in the affected region. He also had radiographic changes in his sacro-iliac joints compatible with ankylosing spondylitis but no clinical evidence of spinal involvement, and his D.A.T. titre was 1/128; late juvenile rheumatoid arthritis could not therefore be excluded.

The two other patients in this group gave agglutination in the D.A.T. at a titre of 1/32.

Case 2, a man aged 72 years with left granulomatous anterior uveitis, gave a history of generalized polyarthritis lasting 3 months at the age of 43 years, following which he had no further symptoms in the limbs or spine. Examination revealed moderate restriction of movement of his whole spine but no abnormality of limb joints. The erythrocyte sedimentation rate was normal. Radiographically both sacro-iliac joints were abnormal, the disk spaces in the lumbar and cervical regions were greatly narrowed, and there was much new bone formation on the vertebral bodies; the spinal appearances were compatible with healing following an acute process mainly involving destruction of intervertebral disks. The D.A.T. result suggested that this might have been a rheumatoid episode in which the spine was principally involved, but the gonococcal complement-fixation test was also doubtfully positive so that Reiter's disease of venereal origin had to be considered a possibility, though there was no history of genito-urinary infection.

Case 3, a man aged 49 years, with left anterior uveitis of doubtful type, gave a history of mild low back pain in his 'teens and of pains and increasing deformity in the dorsal region for 4 years. He had a virtually rigid spine, with limited chest expansion and hypermobility of wrist tarsal and knee joints. His erythrocyte sedimen-

TABLE IV

OSTEO-ARTHRITIS AND RHEUMATOID ARTHRITIS

Aetiology of Uveitis		Unknown		Non-rheumatic		Total	
		Number	Per cent.	Number	Per cent.	Number	Per cent.
Examined for Rheumatic Disease ..		184	100	25	100	209	100
Osteo-Arthritis	Generalized	25	13·6	3	12·0	28	13·4
	Degenerative disease ..	16	8·6	3	12·0	19	9·1
	Total	41	22·2	6	24·0	47	22·5
Rheumatoid Arthritis		20	10·9	2	8·0	22	10·5

tation rate was 20 mm./hr (Wintrobe). He had severe valvular heart disease and no further investigations were made as he died suddenly from cardiac causes. The most probable diagnosis appeared to be ankylosing spondylitis with coincident rheumatic heart disease.

Twelve patients who were not examined for rheumatic disease had the D.A.T. performed. In two patients the test was positive. One of these gave a vague history of muscle pains, but had no trouble at the time of onset of uveitis; the other gave no history of rheumatism, but suffered from psoriasis and lupus vulgaris.

The incidence of rheumatoid arthritis in the 209 patients examined for rheumatic disease was therefore 10·5 per cent.; in the 221 patients who had some sort of investigation for rheumatoid arthritis, the incidence was 11·5 per cent.

The incidence of rheumatoid arthritis in patients with uveitis of known non-rheumatic origin is shown in Table IV; it is not significantly increased in the patients with no obvious cause for the uveitis. Further analysis, taking into account the age distribution of the patients with rheumatoid arthritis, and after exclusion of patients with spondylitis or Reiter's disease in whom the additional diagnosis of rheumatoid arthritis was unlikely to be made, also failed to reveal any significant difference in incidence of rheumatoid arthritis in the groups of patients with and without a known cause for their uveitis.

In the survey of the general population of Leigh in the age groups 55-64 years (Kellgren, 1955) the incidence of all grades of rheumatoid arthritis was found to be 5 per cent. in males and 18 per cent. in females. One of the thirteen males and two of the twelve females in this age group in the present series had rheumatoid arthritis. The numbers of uveitis patients in this age group are small but these findings do not suggest an unduly high incidence of rheumatoid arthritis.

Sheep Cell Differential Agglutination Test.—This test was performed in 190 patients, 178 of whom were examined for rheumatic disease. Details of these patients are given in Table V.

In the subjects tested in the Leigh survey, seven of the 256 with no clinical evidence of rheumatoid arthritis and twelve of the 94 with such evidence gave positive tests (Ball, 1955). The figures for the uveitis patients are not significantly different from these but strict comparison of these groups is not possible since the uveitis patients were on the whole younger. Three of the six uveitis patients with positive tests classed as having "clinical R.A." in Table IV had atypical spondylitis as described above and at least two of them would not have been diagnosed clinically as rheumatoid arthritis. If these three patients are placed in the group with "No clinical R.A.", there is still no significant difference from the Leigh survey.

TABLE V

SHEEP CELL DIFFERENTIAL AGGLUTINATION TEST

Number of Patients		Differential Agglutination Test	
		Number Tested	Number Positive
Whole Series	237	190	10
Not Examined for Rheumatic Disease	28	12	2
Examined for Rheumatic Disease	209	178	8
Clinical Rheumatoid Arthritis (all grades)	21	20	6
No Clinical Rheumatoid Arthritis	188	158	2

REITER'S DISEASE.—Some features of the sixteen patients to whom this diagnosis was applied with various degrees of assurance are set out in Table VI.

TABLE VI

REITER'S DISEASE

Radiographic Changes	Patients			Uveitis	Genito-urinary	Dysentery	Arthritis
	Male	Female	Total				
Present ..	5	3	8	8	6	2	8
Absent ..	2	6	8	8	8	0	5

Table VII (overleaf) gives more detailed information regarding eight cases (Cases 4 to 11) with radiographic changes in the spine or sacro-iliac joints.

With Radiographic Changes.—In Cases 8 and 11 (Table VII) the three components of the syndrome had occurred simultaneously, and in five of the others, two components had occurred simultaneously at least once during the course of the illness; in Case 7 the history was unreliable. The long duration of the illness is noteworthy.

In Cases 4 to 6 the disease appeared to be of venereal origin, and there was almost certain evidence in Case 5 and suggestive evidence in the others that the original urethritis was not straightforward gonorrhoea. In two other male patients, dysentery was a possibility, though one of these had a positive gonococcal complement-fixation test.

The mode of infection in the females was less obvious. Ankylosing spondylitis was an alternative diagnosis in Case 10, as was Behcet's disease in Case 11.

The uveitis was never the initial manifestation, and was anterior in all cases. It was associated with superficial punctate keratitis in one patient, who was therefore also included in the group with uveitis of non-rheumatic origin. This finding is of interest in view of the possible virus aetiology of both Reiter's disease (Dunham, Rock, and Belt, 1947; Harkness, 1950) and some types of superficial punctate keratitis (Braley and Alexander, 1953). Relapse of the uveitis was not associated with recurrence of the keratitis.

Without Radiographic Changes.—In one female patient the three components of the syndrome occurred simultaneously; she had dysuria, frequency and vaginal discharge for 4½ months, and non-granulomatous posterior uveitis and retinal perivasculitis for 4 months; she had pain in the back and one finger, and sacro-iliac joint tests were positive.

TABLE VII

REITER'S DISEASE WITH RADIOGRAPHIC CHANGES IN SACRO-ILIAC JOINTS OR SPINE

Case	Sex	Age		Onset	Manifestations			Erythrocyte Sedimentation Rate	Gonococcal Complement fixation Test	Differential Agglutination Test	Radiographs
		Onset	Attending		Uveitis	Genito-Urinary	Arthritis				
4	M	30	50	Urethritis and arthritis	Recurrent non-granulomatous anterior uveitis from age 46	Urethritis; gross haematuria	Feet, knees, low back at age 30; painful heel at age 46	5	—	1/4	Right calcaneal periostitis ++. Sacro-iliac joints abnormal
5	M	25	33	Urethritis	Anterior uveitis, doubtful type, present 3 wks. ?Previous attack age 29	Recurrent urethritis	"Penicillin resistant gonococcal arthritis", mainly feet and back at age 25; recurrence at age 29	24	Doubtful	1/8	Calcaneal spur. Arthritis great toes and right sacro-iliac joints. Early marginal bridging lower dorsal disk spaces
6	M	24	62	Urethritis	Recurrent non-granulomatous anterior uveitis from age 26	Prolonged urethritis	Feet, ankles, knees for 18 months at age 28; feet, knees, odd fingers, and shoulders for 1 year at age 32	40	Neg.	0	Changes in feet, knees and spine
7	M	19	58	Severe recurrent diarrhoea	Anterior uveitis, doubtful type, present 10 days, first attack	Positive gonococcal complement-fixation test	Feet at age 55; gross restriction lower spine	15	+	1/8	Arthritis feet and sacro-iliac joints; ligamentous ossification spine
8	F	"30s"	53	Pain in lumbar region and left knee	Anterior uveitis, doubtful type, present 1 month, first attack	Vaginal discharge for 18 months; severe cystitis for 4 weeks one year ago	Lumbar spine and left knee from "30s"; left acromioclavicular joint for 7 weeks, and neck for one month	5	Neg.	1/8	Calcaneal spurs. Changes in symphysis pubis, pelvis, and spine
9	F	21	48	Painful swelling of knees	Recurrent non-granulomatous kerato-uveitis since age 21	Recurrent cystitis since age 21	Recurrent transient pains (particularly back) since age 21; no objective changes	28	Neg.	0	Borderline abnormality of sacro-iliac joints. Pelvis, hip, knees, and feet normal
10	M	22	38	Dysentery, stiff and painful hips	Non-granulomatous anterior uveitis at age 38	—	Recurrent buttock and groin pain since age 22; back and shoulder pain since age 36	26	Neg.	Neg.	Bilateral sacro-iliac joint sclerosis, compatible with ankylosing spondylitis
11	F	25	31	Sciatica; and aphthous stomatitis	Non-granulomatous kerato-uveitis at age 31	Yellow intermenstrual discharge; nocturnal frequency	Sciatica at age 25; neuritis under one breast for one year; sacro-iliac joint tests positive	3	Neg.	Neg.	Doubtful sclerosis of one sacro-iliac joint

In addition to the uveitis, four of the remaining seven patients had had both genito-urinary symptoms and arthritis during the course of the illness. The group as a whole did not appear homogeneous, and it seemed possible that the various components of the syndrome might in some cases have been associated by chance.

There was no obvious association with any particular type of uveitis; in one case the uveitis began with superficial punctate keratitis.

Spinal Arthritis

Ankylosing Spondylitis.—In 35 of the 38 patients in whom spondylitis was the main diagnosis the picture was typical or suggestive of classical ankylosing spondylitis. Some features of these patients are shown in Table VIII.

Radiographic changes in both sacro-iliac joints compatible with ankylosing spondylitis were present in 22 patients. The disease picture in the patient whose serum gave a positive result in the D.A.T. was typical of advanced ankylosing spondylitis, and he had been treated by deep *x* rays 4 years previously with great benefit. In five patients the spondylitis, which was of many years' duration, had resulted in obvious spinal rigidity, and in ten others clinical examination strongly suggested the diagnosis. Although mild symptoms of spondylitis had been present for from 4 to 12 years in five of the seven remaining patients, in two the spinal symptoms had been so mild that they had never consulted a doctor about them, and only one had diminished spinal movements and chest expansion; in these patients the diagnosis was usually suspected from the history of recurrent "lumbago", "sciatica", or "fibrositis", particularly when these symptoms were aggravated by immobility, and was confirmed by radiography of the sacro-iliac joints. Two patients gave a history of an initial attack of uveitis that had preceded pain or stiffness in the trunk or limbs by as long as 4 years.

It might be expected that uveitis associated with ankylosing spondylitis would occur during the active phases of the disease, but the spinal disease was judged to be inactive on clinical grounds in one-third of the 22 patients. The level of the erythrocyte sedimentation rate was poorly correlated with the clinical assessment of disease activity, being normal in one-third of the patients, including four of the seven in whom the presence of the spinal disease was least obvious; the diagnosis would have been missed in these patients if the erythrocyte sedimentation rate had been used as a screening test. Judged by either criterion, therefore, it would appear that uveitis may occur during an apparently inactive phase of the spondylitis in a substantial proportion of patients.

The uveitis in these 22 patients was anterior, without involvement of the cornea or choroid, and was non-granulomatous apart from three doubtful cases, and all the patients presented with active disease in one eye only. Eight patients (36·4 per cent.) had had previous attacks of uveitis; in two both eyes had been affected, in four the same eye, and in two the opposite eye. This incidence of previous attacks is not significantly higher than that (24·4 per cent.) in the patients with the non-granulomatous type of anterior uveitis as a whole.

The thirteen remaining patients without radiographic evidence of ankylosing spondylitis all had clinical findings suggestive of ankylosing spondylitis, but the sacro-iliac joints appeared normal in eleven of the twelve patients with radiographs, and in the remaining patient there was probable erosion of one joint only. Five had symptomless restriction of movement of the lower spine, and only two, both men aged 60 years, had had spinal pain of any note; one of them had considerable limitation of movement of his whole spine. The distribution of their

TABLE VIII

SPINAL ARTHRITIS

Spondylitis		No. of Patients			Erythrocyte Sedimentation Rate		Differential Agglutination Test		Type of Uveitis			History of Previous Uveitis
		Male	Female	Total	Done	Elevated	Done	Positive	Granulomatous	Non-granulomatous	Doubtful	
Ankylosing	With radiographic confirmation ..	19	3	22	20	13	18	1	0	19	3	8
	Without radiographic confirmation ..	10	3	13	13	2	12	0	0	10	3	5
Atypical	Rheumatoid Arthritis	3	0	3	3	2	3	3	1	1	1	1
	Reiter's Disease ..	5	3	8	8	5	8	0	0	5	3	3
	Miscellaneous ..	2	2	4	3	3	1	0	0	3	1	0

ages of attendance suggested that the thirteen patients fell into two groups, one mainly in the fourth and the other mainly in the sixth decade. When these patients were seen it appeared possible from the clinical picture that the uveitis might be the presenting or initial manifestation of ankylosing spondylitis and that they might subsequently develop diagnostic changes, but this supposition is unlikely to be correct in the older patients. Although the uveitis was of the non-granulomatous variety in at least ten of these thirteen patients, in one the whole uveal tract was affected, and in three the cornea, one having a dendritic ulcer of definite virus aetiology; this is in contrast to the involvement of iris and ciliary body only in the patients with radiographic evidence of ankylosing spondylitis.

"Atypical" Spondylitis.—This group, further details of which are given in Table VIII, was formed by three patients who have already been described in the rheumatoid arthritis group, eight from the Reiter's disease group, and four who form a miscellaneous group. Two of the latter were males with non-granulomatous anterior uveitis in whom ankylosing spondylitis appeared a distinct possibility, but in both the radiographic appearances were unusual, and one gave a history of pain and swelling of the knee and wrist in India 7 years previously, which was suggestive of Reiter's disease, although there was no history of genito-urinary infection or dysentery. One of the two remaining patients was a female aged 46 years with right non-granulomatous anterior uveitis, clinical and doubtful radiographic evidence of arthritis of one sacro-iliac joint, and painful swelling of one ankle of 2 years' duration, in whom no definite diagnosis was established; the other is described below (Case 12).

Case 12, a female aged 62 years, with valvular heart disease, the second patient in the series in whom valvular heart disease was associated with spondylitis, had anterior uveitis of doubtful type. Some 20 years previously she had had a generalized polyarthritis lasting some weeks with residual pains in the feet for one year. Thereafter she had suffered recurrent pains in the limbs and spine and had developed Heberden's nodes and bony enlargement of other finger joints. The spinal curves were increased, the dorsal kyphos being fixed, and cervical and lumbar movements moderately restricted. The erythrocyte sedimentation rate was 17 mm./hr (Wintrobe) and the D.A.T. was negative. Radiographs revealed erosion and sclerosis of the sacro-iliac joints and symphysis pubis, the former being practically fused; the joint spaces in both hips were decreased, the femoral heads having a globular appearance. There was evidence of disk degeneration in the lumbar and cervical regions of the spine and of osteo-arthritis in the hands, feet, and knees. The changes in the limb joints suggested "generalized" or secondary osteo-arthritis, but those in the sacro-iliac joints, symphysis pubis, and hip joints were of the type occasionally observed after prolonged rheumatic fever in adult life (Thomas, 1955; Sharp, 1955).

Ankylosing spondylitis could not be definitely excluded in any of the five males; the uveitis was non-granulomatous in four of these and was of doubtful type in the fifth. In the whole group of fifteen patients, the uveitis was definitely non-granulomatous in nine, and granulomatous in only one.

OTHER DISEASES.—Psoriasis was encountered in two patients with no disease of the limb or spine, and also in one with degenerative disease of the spine and one knee, one with rheumatoid arthritis, and another with ankylosing spondylitis. In addition there was one elderly man with psoriasis, who did not attend for examination of the joints, who also had lupus vulgaris and a strongly positive D.A.T.; he has been mentioned previously in the section on rheumatoid arthritis. The incidence of psoriasis was therefore 2·5 per cent.; Ingram (1954) has estimated that psoriasis occurs in 1 to 2 per cent. of the general population.

Two patients with valvular heart disease and spinal disease have already been described. Four other patients with valvular lesions gave a history of rheumatic fever: three had no abnormalities in the spine or limbs, and the fourth had radiographic evidence of neoplastic changes in the pelvis and spine. No suitable figures of the incidence of rheumatic heart disease in the general population in this region are available for comparison. Acute rheumatic fever was not encountered.

Polyarteritis nodosa was suspected in one elderly woman who had necrotic ulcers on her legs and feet, and in another woman, already included in the section on osteo-arthritis, who had multiple symptoms and acute arthritis of one wrist associated with degenerative disease of the spine.

A male aged 33 years and a female aged 23 years both gave a history of pain and stiffness in the knees some years previously, suggestive of Reiter's disease, but there was no history of genito-urinary infection or dysentery; the joints were clinically normal and radiographs were not available.

Finally, there were four female patients who had in common Raynaud s attacks in the extremities, but no other evidence of rheumatic disease, and six patients with spinal deformities.

Discussion

In this survey, there did not appear to be any particular association between uveitis and psoriasis,

acute rheumatic fever, generalized osteo-arthritis, or degenerative disease of the limbs and spine.

The failure to find any significant association of rheumatoid arthritis with uveitis is of greater interest, although undoubtedly patients may occasionally be encountered in whom the uveitis is associated with changes in the cornea and sclera similar to those in the connective tissues elsewhere in rheumatoid arthritis; one of our patients, a female aged 54 years, had intractable bilateral granulomatous uveitis and nodular sclero-keratitis associated with severe rheumatoid arthritis with multiple subcutaneous nodules and marked spinal involvement. An association between uveitis and Still's disease is also not excluded. In the majority of patients with uveitis and rheumatoid arthritis, however, the association appears likely to be coincidental.

The higher incidence of rheumatoid arthritis and the absence of Reiter's disease in the series of patients with uveitis reported in the literature may be due to differences in diagnostic criteria. The high proportion of the series of patients reported by Vesterdal (1951) who had arthritis associated with "gonorrhoea", and the association of genito-urinary infection with ankylosing spondylitis in the majority of the patients of Romanus (1953) probably indicate that many of their cases would have been placed in the category of Reiter's disease in the present study. In the older literature, rigidity of the spine (Brodhurst, 1866; Rendu, 1899; Launois, 1899) and involvement of the sacro-iliac joints (Raymond, 1899; Galliard, 1899) in a polyarthritis associated with urethritis has occasionally been mentioned. Harkness (1950) produced convincing evidence that the urethritis is in many instances non-specific and of venereal origin. Ford (1953), in a study of 21 patients with arthritis following venereal urethritis, found four who had apparently developed ankylosing spondylitis. Harkness also suggested that the same infective agent might be responsible for the very similar syndrome following dysentery (Fiessinger and Leroy, 1916; Reiter, 1916; Paronen, 1948), the portal of entry in these cases being the diseased intestinal mucous membrane. Marche (1951) has reported that the clinical picture of ankylosing spondylitis may also develop in the dysenteric form of the syndrome.

Our findings confirm the association of unilateral non-granulomatous anterior uveitis with ankylosing spondylitis of which it may be the initial symptom. In only three of the patients suffering from ankylosing spondylitis with radiographic confirmation was the uveitis of the doubtful type, and granulomatous uveitis was not seen in any of them. Ankylosing spondylitis occurred in 30·8 per cent. of the males and in 22·6 per cent. of all the patients with non-granulomatous anterior uveitis examined for rheumatic disease; the total incidence of ankylosing spondylitis, including those patients with atypical spondylitis in whom ankylosing spondylitis could not be definitely excluded, may have been as high as 49·0 per cent. in males and 35·6 per cent. in all patients with this type of uveitis. The incidence in uveitis of the doubtful type was about half that in the non-granulomatous type. The failure of some previous observers to find a marked association of uveitis and ankylosing spondylitis might be due to the relative mildness of the rheumatic symptoms in many cases, so that the diagnosis requires full clinical and radiological examination.

Non-granulomatous anterior uveitis was found to be associated with rheumatic diseases in which involvement of the spine was a feature, namely spinal arthritis and Reiter's disease. This raises the possibility of a connexion between this type of uveitis and a factor common to these rheumatic diseases which is perhaps related to the spinal involvement. In uveitis as a whole, these diseases occurred in about one patient in four.

Summary

(1) 209 out of 237 consecutive patients with uveitis were examined for rheumatic diseases. The sheep cell differential agglutination test was performed on 190 of the patients, including 178 of those examined.

(2) Uveitis was found to be specially associated with Reiter's disease (often with spinal involvement), ankylosing spondylitis, and some other forms of spondylitis. The uveitis was almost entirely of the unilateral non-granulomatous anterior type, and a history of previous uveitis was no more frequent than in other patients with non-granulomatous uveitis.

(3) The association of uveitis with other rheumatic diseases appeared to be coincidental, except in one patient with nodular sclero-kerato-uveitis and severe rheumatoid disease.

(4) The ankylosing spondylitis was sometimes very mild and apparently inactive; in two patients, uveitis was the initial complaint.

Prof. J. H. Kellgren examined many of these patients, and we are indebted to him and to Mr. O. M. Duthie for much valuable advice. Dr. J. Ball performed all the sheep cell agglutination tests, and gave much help in the interpretation of the results. We are also indebted to Dr. Robert Ollerenshaw and his staff in the Medical Illustration Department for reproducing the figure.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.
—— (1955). Personal communication.
Bartoš, J. (1952) *Čsl. ofthal.*, **8**, 28. (*Abs. in Ophthal. Lit.* (*Lond.*) (1952). **6**, p. 63, No. 133.)
Bauer, W. (1938). Personal communication, *quoted by* Berens and others (1942).
Bennett, G. (1955). *Brit. J. Ophthal.*, **39**, 727.
Berens, C., Rothbard, S., and Angevine, D. M. (1942). *Amer. J. Ophthal.*, **25**, 295.
Bernstein, L., and Broch, O. J. (1949). *Acta med. scand.*, **135**, 185.
Birkbeck, M. Q., Buckler, W. S. J., Mason, R. M., and Tegner, W. S. (1951). *Lancet*, **2**, 802.
Braley, A. E., and Alexander, R. C. (1953). *A.M.A. Arch. Ophthal.*, **50**, 147.
Brodhurst, B. E. (1866). *In* Reynolds, J. Russell, "A System of Medicine", vol. 1, p. 920. Macmillan, London.
Coburn, A. F. (1931). "The Factor of Infection in the Rheumatic State", p. 24. Baillière, Tindall and Cox, London.
Dunham, J., Rock, J., and Belt, E. (1947). *J. Urol.*, **58**, 212.
Duthie, J. J. R. (1955). Personal communication.
Fiessinger, N., and Leroy, E. (1916). *Bull Soc. méd. Hôp. Paris*, 3 sér., **40**, 2030.
Fischer, A., and Vontz, O. (1932). *Mitt. Grenzgeb. Med. Chir.*, **42**, 586.
Ford, D. K. (1953). *Annals of the Rheumatic Diseases*, **12**, 177.
Forestier, J. *Quoted by* Romanns (1953).
Galliard, L. (1899). *Bull. Soc. méd. Hôp. Paris*, **16** (3 sér.), 408.
Golding, F. C. (1936). *Brit. J. Surg.*, **23**, 484.
Godtfredsen, E. (1949). *Brit. J. Ophthal.*, **33**, 261.
Guyton, J. S., and Woods, A. C. (1941). *Arch. ophthal.* (*Chicago*), **26**, 983.
Harkness, A. H. (1950). "Non-Gonococcal Urethritis", p. 99. Livingstone, Edinburgh.
Hart, F. Dudley (1951). *Trans. ophthal. Soc. U.K.*, **71**, 167.
——, Robinson, K. C., Allchin, F. M., and Maclagan, N. F. (1949). *Quart. J. Med.*, **18**, 217.
—— (1955). *Annals of the Rheumatic Diseases*, **14**, 77.
Hench, P. S., Slocumb, C. H., and Polley, H. F. (1947). *Med. Clin. N. Amer.*, **31**, 879.
Ingram, J. T. (1954). *Brit. med. J.*, **2**, 823.
Kellgren, J. H. (1955). Personal communication.
——, and Moore, R. (1952). *Brit. med. J.*, **1**, 181.
Launois, P. E. (1899). *Bull. Soc. méd. Hôp. Paris*, **16**, 736.
Lawrence, J. S. (1955). Personal communication.
Marche, J. (1951). "II Congr. Europeo de Reumatologia, 1951. Comunicaciones", p. 14. Barcelona, 14.
Marchin, P. de (1954). *Rev. Rhum.*, **21**, 531.
Marie, P., and Lèri (1899). *Bull. Soc. méd. Hôp Paris*, **16**, 237.
Michaud, P., and Forestier, J. (1954). *Ibid.*, **21**, 487.
Mowbray, R., Latner, A. L., and Middlemiss, J. H. (1949). *Quart. J. Med.*, **18**, 187.
Müller, H. (1949). *Ber. dtsch. ophthal. Ges. Heidelberg.*, **55**, 113.
Nutt, A. B. (1951). *Trans. ophthal. Soc. U.K.*, **71**, 149.
Paronen, I. (1948). *Acta med. scand.*, Suppl. 212.
Parr, L. J. A., White, P., and Shipton, E. (1951). *Med. J. Aust.*, **1**, 544.
Piora, J. (1953). *Acta med. scand.*, **144**, 284.
Polley, H. F., and Slocumb, C. H. (1947). *Ann. intern. Med.*, **26**, 240.
Raymond, —. (1899). *In discussion of* Marie and Leri (1899).
Reiter, H. (1916). *Dtsch. med. Wschr.*, **42**, 1535.
Rendu, —. (1899). *In discussion of* Galliard (1899), p. 411.
Romanus, R. (1953). *Acta med. scand.*, Suppl. 280.
Rudolph, C. J. (1945). *Amer. J. Ophthal.*, **28**, 319.
Schley, H. (1937). *Klin. Mbl. Augenheilk.*, **98**, 780.
Schöne, R., and Steen, E. (1951). *Acta ophthal.* (*Kbh.*), **29**, 201.
Scott, S. G. (1942). "A Monograph on Adolescent Spondylitis or Ankylosing Spondylitis." Oxford University Press, London.
Sharp, J. (1955). *Lancet*, **2**, 1371.
——, and Easson, E. C. (1954). *Brit. med. J.*, **1**, 619.
Sorsby, A., and Gormaz, A. (1946). *Ibid.*, **1**, 597.
Teschendorf, H. J. (1933). *Dtsch. med. Wschr.*, **59**, 1576.
Thomas, A. E. (1955). *Annals of the Rheumatic Diseases*, 14, 259.
Vesterdal, E. (1951). *Acta ophthal.* (*Kbh.*), **29**, 509.
West, H. F. (1949). *Annals ot the Rheumatic Diseases*, **8**, 143.
Zewi, M. (1947). *Acta ophthal.* (*Kbh.*), **25**, 47.

L'uvéite et les maladies rhumatismales

Résumé

(1) 209 d'entre 237 malades consécutifs, atteints d'uvéité, furent examinés pour des maladies rhumatismales. Chez 190 malades, comprenant 178 de ceux examinés, on effectua la réaction d'agglutination differentielle des cellules de mouton.

(2) On constata que l'uvéite était particulièrement associée avec la maladie de Reiter (souvent avec des implications vertébrales), la spondylarthrite ankylosante et certaines autres formes de spondylite. L'uvéite était presque toujours du type antérieur, unilatéral et non-granulomateux et une uvéite antécédante n'était pas plus fréquente que chez d'autres malades atteints d'uvéite non-granulomateuse.

(3) L'association de l'uvéite avec d'autres maladies rhumatismales apparût être fortuite, excepté chez un des malades atteint de scléro-kérato-uvéite nodulaire et d'une sévère maladie rhumatismale.

(4) La spondylarthrite ankylosante était parfois très légère et apparemment inactive; chez deux malades l'uvéite était la maladie initiale.

La uveitis y las enfermedades reumáticas

Sumario

(1) De 237 enfermos consecutivos afectos de uveitis, 209 fueron investigados en busca de enfermedades reumáticas. En 190 enfermos, comprendiendo 178 de los investigados, se hizo la reacción de aglutinación diferencial de las células de oveja.

(2) Se halló que la uveitis fué particularmente asociada con la enfermedad de Reiter (a menudo con implicaciones vertebrales), la espondilartritis anquilosante y ciertas otras formas de espondilitis. La uveitis fué casi siempre del tipo anterior, unilateral y agranulomatosa y una uveitis antecedente no fué más frecuente que en otros enfermos con uveitis agranulomatosa.

(3) La asociación de la uveitis con otras enfermedades reumáticas pareció ser fortuita, con la excepción de un enfermo con esclero-querato-uveitis nodular y con una enfermedad reumática grave.

(4) La espondilartritis anquilosante fué a veces muy leve y aparentemente inactiva; en dos enfermos la uveitis fué la enfermedad inicial.

Ann. rheum. Dis. (1956), **15**, 151.

HAEMODILUTION IN RHEUMATOID DISEASE

BY

M. R. JEFFREY

From the Rheumatism Research Unit of the South West Region, Royal National Hospital for Rheumatic Diseases, Bath

(RECEIVED FOR PUBLICATION FEBRUARY 27, 1956)

It has been suggested (Robinson, 1943; Dixon, Ramcharan, and Ropes, 1955) that the plasma volume in rheumatoid disease is greater than normal and that this increase may produce anaemia by dilution of the red cell mass. Such a mechanism might account for the refractory anaemia which sometimes occurs and in which there is a proportionate reduction of red cells and haemoglobin in the peripheral blood, the size and haemoglobin content of the individual red cell being essentially normal. Clearly, haemodilution does not explain the presence of hypochromic or microcytic red cells, nor the anaemia which responds to iron therapy; its possible role in the genesis of refractory anaemia, however, seemed to merit further investigation.

The blood, plasma, and cell volumes of groups of rheumatoid patients and of haematologically normal controls have therefore been estimated. As the blood volume is known to be influenced by sex, age, and bodily configuration, the controls were selected so that, in terms of these factors, the control and rheumatoid groups were as nearly alike as possible. The results of the investigation do not indicate that haemodilution is a factor of importance in the genesis of anaemia in rheumatoid disease.

Material and Methods

(1) Patients Investigated.—The patients suffered from typical rheumatoid disease uncomplicated by blood loss or other conditions liable to affect haemopoiesis. So that surface area could be estimated from their height and weight, only ambulant patients, free from flexion deformities of the lower limbs and spine, were investigated. Volume estimations were made before any therapy, other than physiotherapy and simple analgesics, had been given. The controls were a mixture of healthy hospital workers and of patients who had locomotor disorders not likely to affect haemopoiesis, *e.g.* local osteo-arthritis, prolapsed disk, or psychogenic rheumatism; all had normal haemoglobin levels and sedimentation rates.

(2) Comparability of Groups.—There were 42 controls (20 male and 22 female) and 88 rheumatoid patients (35 male and 53 female). Their average weights, surface areas, and ages are shown in Table I, and their distributions by weight in Table II. The mean values and

TABLE I

WEIGHT, SURFACE AREA, AND AGE. MEAN VALUES

Sex	Group	No. of Cases	Bodyweight (kg.)		Surface Area (sq. m.)		Age (yrs)	
			Mean	S.E.	Mean	S.E.	Mean	S.E.
Male	Control	20	66·5	2·0	1·78	0·03	50·8	3·0
	Rheumatoid ..	35	65·0	1·7	1·75	0·03	49·8	1·8
Female	Control	22	58·0	1·8	1·54	0·03	43·9	2·4
	Rheumatoid ..	53	54·5	1·2	1·56	0·02	47·8	1·6

TABLE II

DISTRIBUTION BY WEIGHT

Bodyweight (kg.)		40–49	50–59	60–69	70–79	80–89
Male	Control	—	6	6	6	2
	Rheumatoid ..	—	12	10	10	3
Female	Control	5	9	6	2	—
	Rheumatoid ..	19	20	11	3	—

distributions of relevant groups agree quite closely, except for a difference of 3·5 kg. in the weights of the women, produced by an excess of "light-weights" in the rheumatoid group. Distributions by age and surface area are not shown, but were quite closely comparable; plotting the results of volume estimations against age revealed no material association in the range of ages studied here and the effects of age are therefore disregarded hereafter.

(3) Techniques.—Volume estimations were performed at about 12 noon, after the subjects had undertaken a normal morning's programme of work or physical treatment and had then rested for about 20 minutes. The technique employed was that of Gregersen (1944), in which a known volume of dye (Evans blue) is injected intravenously and the concentration of the dye in plasma withdrawn 10 minutes later is compared photometrically with a standard, consisting of a known dilution of the dye in the patient's dye-free plasma. The examination of a single 10-minute specimen was considered adequate, as we have found that duplicate estimations by this technique regularly agree to within 5 per cent. Greater accuracy can be achieved by taking several specimens at intervals and retropolating the best fitting line through the observed optical densities to zero time. However, the mingling of the dye in the blood stream is complete in less than 10 minutes and its removal from the plasma proceeds at a slow and steady rate after injection. The rate of removal is slightly greater in rheumatoid disease than in health (Dixon and others, 1955), but the difference is not large enough to introduce an important error after 10 minutes; it would merely tend to produce a slight over-estimate of the rheumatoid plasma volumes. As this was an essentially comparative study, the examination of several specimens after injection was thought unnecessary.

Blood and cell volumes were calculated from the plasma volume and haematocrit. Haematocrits were estimated in duplicate, spun at 3,000 r.p.m. in a radius of 14·5 cm. until the cell volume became constant; readings were corrected for trapped plasma by the graph of Chaplin and Mollison (1952) and for the difference between whole body and venous haematocrits by the factor 0·91 of Chaplin, Mollison, and Vetter (1953). Heparin was the anticoagulant throughout, except for the Westergren erythrocyte sedimentation rate estimations, when 3·8 per cent. sodium citrate was used. Haemoglobin was measured by the cyanhaematin technique of King and Gilchrist (1947). The probability of differences between mean values being due to chance was computed from the "*t*" test for small samples.

Results

Mean values for plasma, cell, and blood volumes in relation to bodyweight and surface area are shown in Table III. In both sexes the rheumatoid patients had considerably lower cell volumes than the controls; the differences are statistically highly significant in relation to weight or surface area. The male rheumatoid patients had a higher mean plasma volume than the controls, the difference reaching statistical significance in relation to surface area. The plasma increase was, however, less than the cell decrease, so that the rheumatoid blood volume was lower than that of the controls, though the difference could quite easily have been fortuitous. In the rheumatoid women the plasma increase was almost the same as the cell decrease, so that their blood volume was the same as that of the controls; the difference in plasma volumes relative to bodyweight was significant.

The relationships between blood, plasma, and cell volumes and bodyweight in the women are displayed in Figs 1, 2, and 3 (opposite and overleaf). The

TABLE III

RELATION OF VOLUMES TO BODYWEIGHT AND SURFACE AREA

Sex	Group		Volumes related to					
			Bodyweight (ml./kg.)			Surface Area (l./sq. m.)		
			Plasma	Cells	Blood	Plasma	Cells	Blood
Male	*Control*	Mean	47·9	32·3	80·2	1·72	1·19	2·91
		S.E. ..	1·8	1·4	3·0	0·05	0·04	0·10
	Rheumatoid	Mean	51·1	24·7	75·8	1·87	0·91	2·78
		S.E. ..	1·5	0·8	2·2	0·05	0·03	0·06
	Significance of difference		0·2	<0·01	0·2	0·05	<0·01	0·3
Female	*Control*	Mean	48·7	26·2	74·9	1·75	0·94	2·69
		S.E. ..	2·3	1·1	3·3	0·07	0·03	0·10
	Rheumatoid	Mean	53·4	22·4	75·8	1·84	0·78	2·62
		S.E. ..	1·4	0·5	1·7	0·03	0·02	0·04
	Significance of Difference		0·05	<0·01	—	0·2	<0·01	—
	Weighted Mean		51·2	21·8	73·0	—	—	—
	Means corrected for Difference in Average Weight		50·9	21·6	72·5	—	—	—

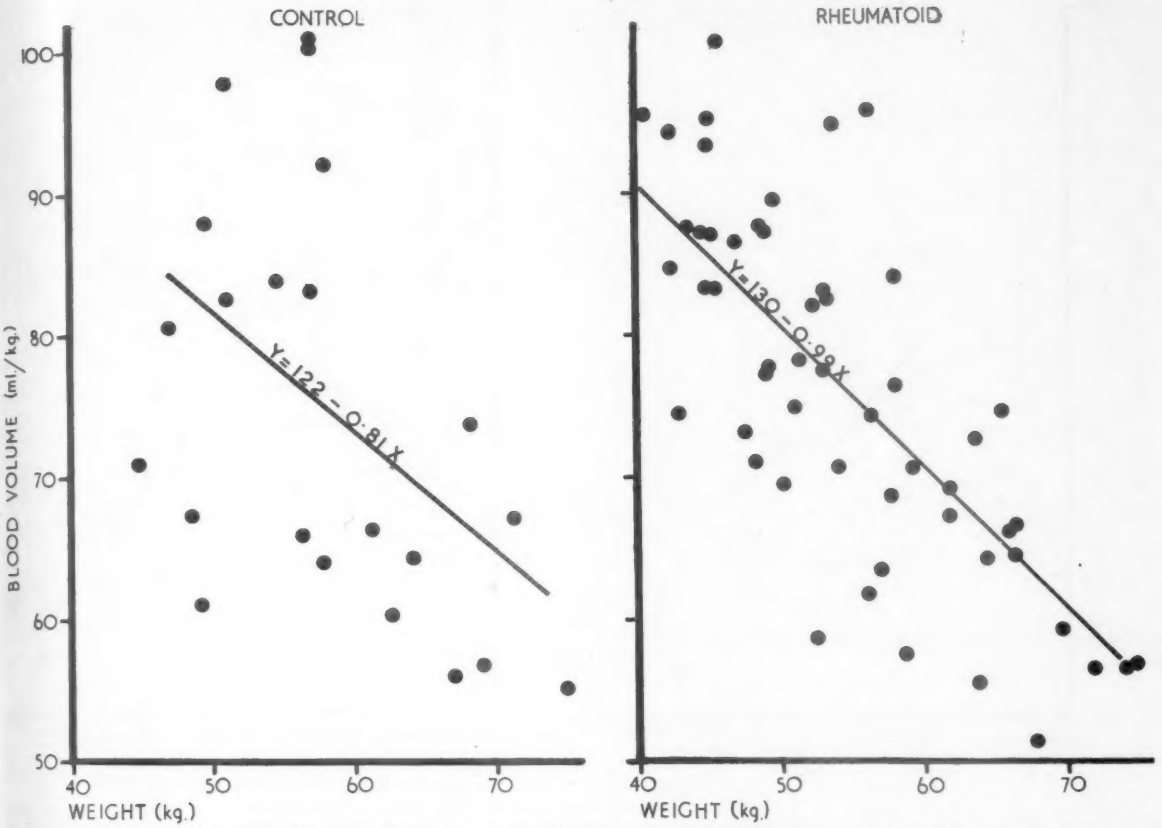


Fig. 1.—Blood volumes of women, plotted as volumes per unit weight (ml./kg.) against weight (kg.). An inverse relationship is suggested Assuming straight-line relationships, the regression equations are as follows:

Control, Volume (ml./kg.) = 122 − 0·81 *x* weight (kg.). S.D. of regression coefficient = 0·37.
Rheumatoid, Volume (ml./kg.) = 130 − 0·99 *x* weight (kg.). S.D. of regression coefficient = 0·14.

men, whose results are not illustrated, exhibited similar trends, which are summarized as regression equations in Table IV. The results are plotted as volumes per unit of weight against weight, as the associations are easier to see in this way.

Both the controls and the patients showed a tendency for the blood and plasma volume per unit bodyweight to decrease rather sharply as weight rose, the association being closest in the case of the plasma volumes of the rheumatoid women. If, for comparative purposes, it is assumed that there is a straight-line relationship between blood and plasma volumes and bodyweight, regression lines may be calculated, of the form $y = a + bx$. The equations, given below Figs 1 and 2, show that there is no great difference between the regression coefficients of the control and rheumatoid groups. The standard errors of the differences between the regression coefficients of the groups are 0·40 and 0·27 for blood and plasma respectively; applying

TABLE IV

REGRESSION EQUATIONS OF BLOOD, PLASMA, AND CELL VOLUMES (ml./kg.) OF MEN UPON BODYWEIGHT (kg.)

Volume	Group	Regression Equations	S.D. of Regression Coefficient
Blood	Control	Volume = 143·4 − 0·95 Wt.	0·28
	Rheumatoid	Volume = 113·9 − 0·59 Wt.	0·18
Plasma	Control	Volume = 82·5 − 0·52 Wt.	0·17
	Rheumatoid	Volume = 79·2 − 0·43 Wt.	0·13
Cells	Control	Volume = 60·0 − 0·42 Wt.	0·13
	Rheumatoid	Volume = 32·8 − 0·12 Wt.	0·08

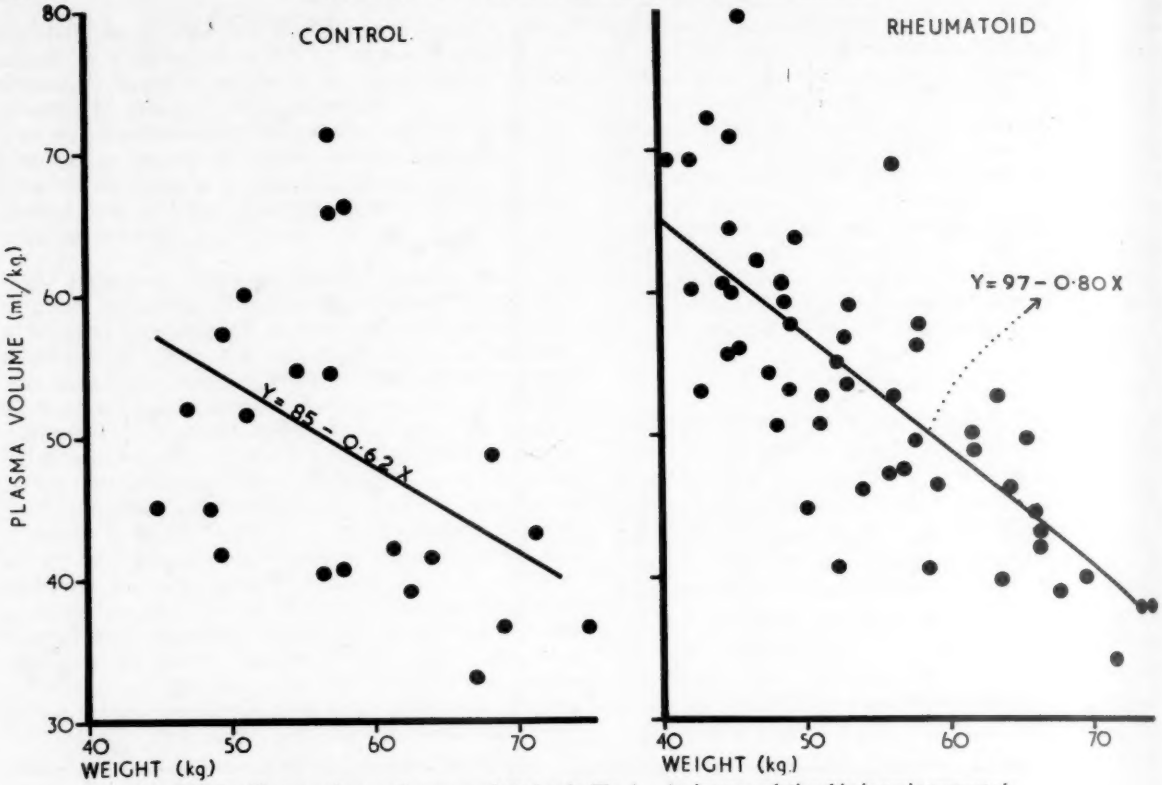


Fig. 2.—Plasma volumes of women, plotted as in Fig. 1. An inverse relationship is again suggested. Assuming straight-line relationships, the regression equations are as follows:
Control, Volume (ml./kg.) = 85 − 0·62 *x* weight (kg.). S.D. of regression coefficient = 0·25.
Rheumatoid, Volume (ml./kg.) = 97 − 0·80 *x* weight (kg.). S.D. of regression coefficient = 0·11.

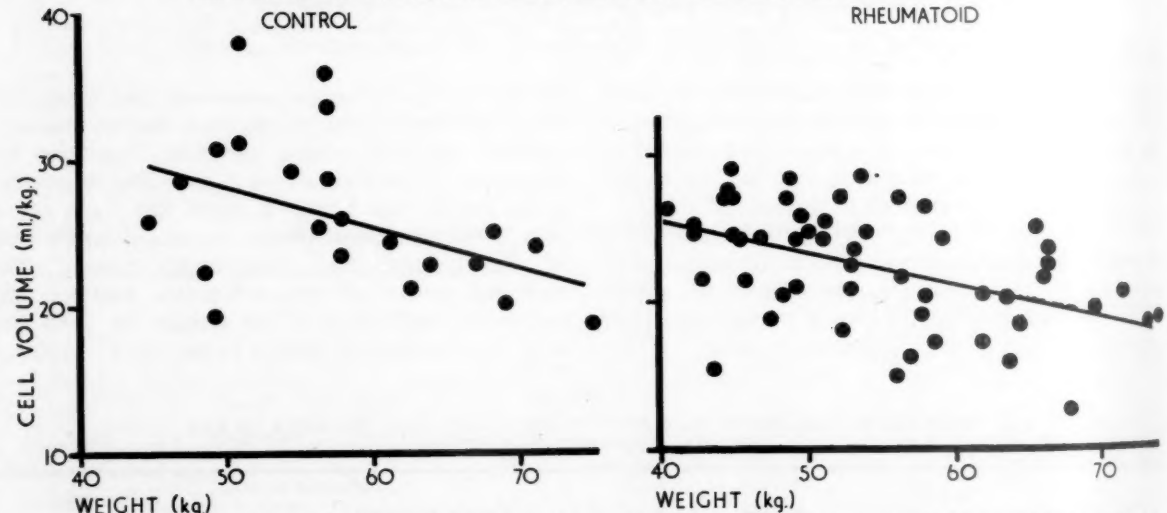


Fig. 3.—Cell volumes of women, plotted as in Fig. 1. There is a slight inverse relationship between cell volume and body weight. The regression equations are as follows:
Control, Volume = 42·2 − 0·28 *x* Wt. S.D. of regression coefficient = 0·13.
Rheumatoid, Volume = 34·4 − 0·22 *x* Wt. S.D. of regression coefficient = 0·17.

the "*t*" test, the values of *p* are found to be 0·7 and 0·5, indicating that the differences could readily be fortuitous. The relation between cell volume and weight was much less, though the trend was in the same direction. Because of these associations and of the excess of female rheumatoid subjects in the

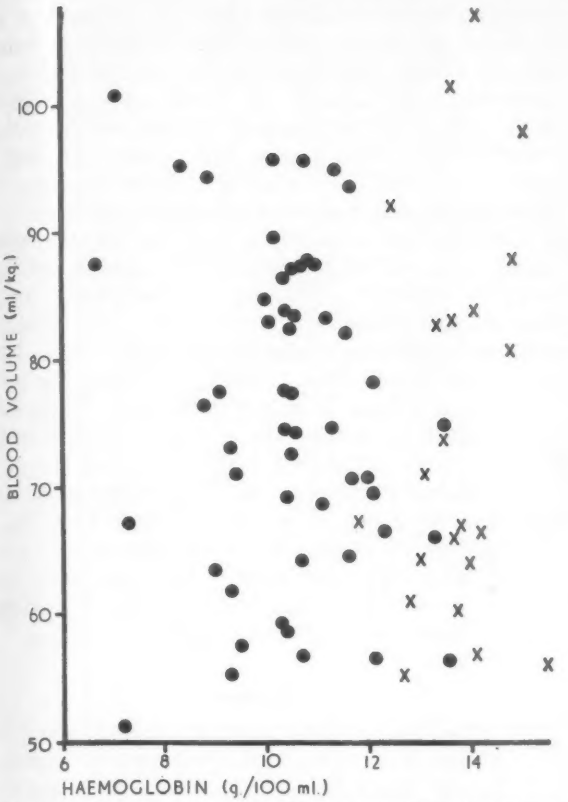


Fig. 4.—Blood volumes of women (ml./kg.) plotted against haemoglobin levels (g./100 ml.). Rheumatoid subjects shown as solid circles, controls as crosses. Wide variations with no clear association.

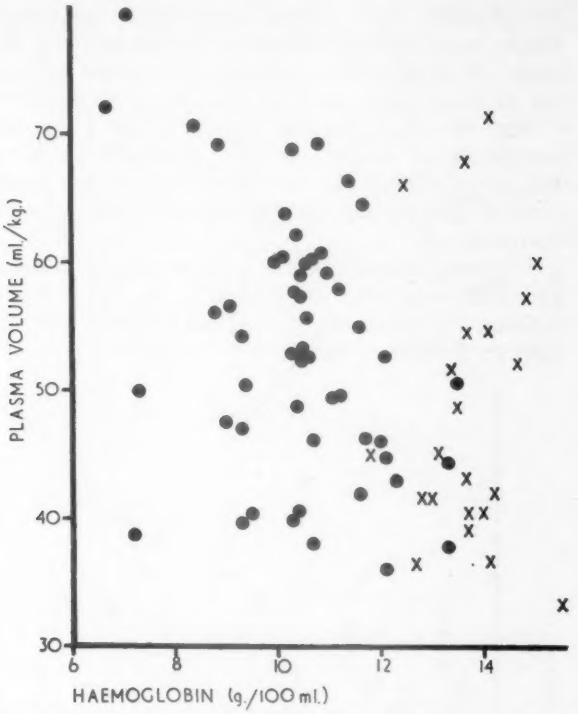


Fig. 5.—Plasma volumes of women (ml./kg.) plotted as in Fig. 4. Wide variations with no clear association.

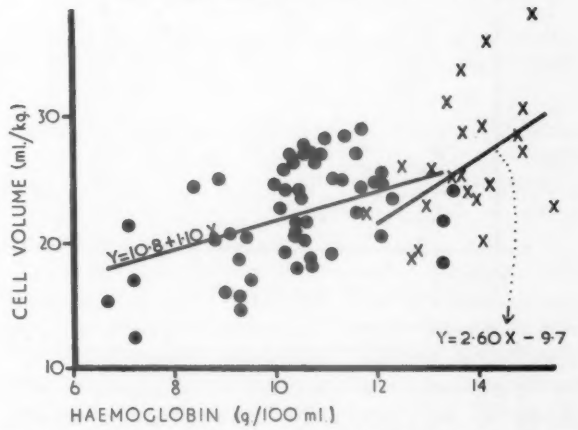


Fig. 6.—Cell volumes of women (ml./kg.) plotted as in Fig. 4. There is a direct and fairly close association between cell volume and haemoglobin level. Assuming a straight-line relationship, the regression equations are as follows:

Control, Volume = 2·60 *x* Hb. (g./100 ml.) − 9·7.
S.D. of regression coefficient = 0·34.

Rheumatoid, Volume = 10·8 + 1·10 *x* Hb. (g./100 ml.).
S.D. of regression coefficient = 0·34.

weight group 40-49 kg., the mean values for the rheumatoid women have been recalculated after adjusting their weight distribution to that of the controls. The resultant weighted means are shown in the penultimate row of Table III; the pattern of changes is similar to that found in the male patients, namely, a marked reduction in cell volume with a smaller increase in plasma and somewhat reduced blood volume.

The relationships between volumes and circulating haemoglobin level are shown in Figs 4, 5, and 6. Blood and plasma show no important relationship to haemoglobin level, but cell volume is directly and quite closely related, and the results from the rheumatoid subjects merge into those of the controls. If a straight-line relationship is assumed and regression lines are calculated, the difference between the regression coefficients of the control and rheumatoid groups is 1·50, and the standard error of the difference is 1·23; the difference could readily be fortuitous ($0{\cdot}3 > P > 0{\cdot}2$).

It seemed possible that the complicating effects of bodyweight might have obscured relationships between blood or plasma volume and haemoglobin level, and that the slightness of the relationship between cell volume and weight was due to varying degrees of anaemia. Accordingly, results were recalculated after constructing regression lines for blood plasma volumes upon weight, and for cell volume upon haemoglobin level, assuming that

straight-line relationships obtained. Individual results were then expressed as differences from the expected values. Plotting these differences against the corresponding haemoglobin levels revealed no closer association than before, but plotting the cell volumes as differences from the values expected from the degree of anaemia did slightly increase the closeness of the association between cell volume and bodyweight.

There was no relationship between plasma volume and disease activity as judged by the erythrocyte sedimentation rate (Fig. 7); blood and cell volumes were similarly unrelated.

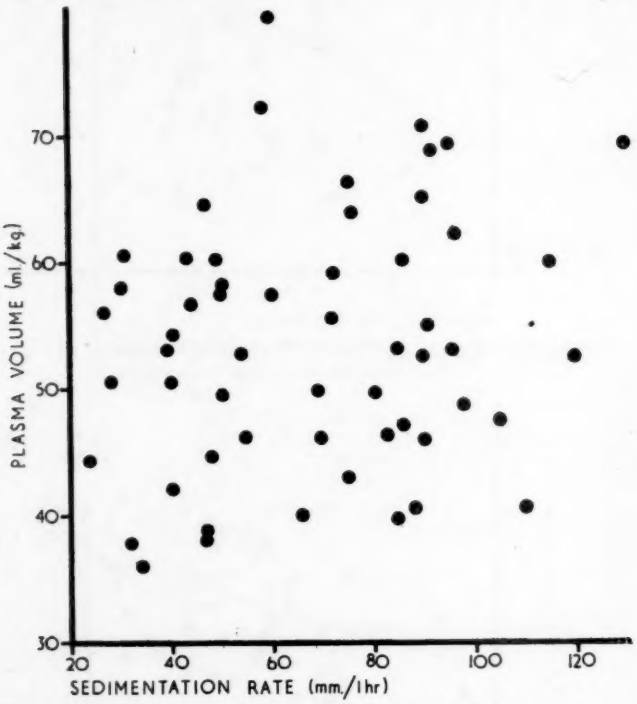


Fig. 7.—Plasma volumes of rheumatoid women (ml./kg.) plotted against erythrocyte sedimentation rates (mm./hr). No relationship.

To exhibit possible differences in volume between anaemic and non-anaemic rheumatoid patients, avoiding the complicating effect of bodyweight, a separate group of non-anaemic female patients whose weights lay between 50 and 60 kg. was examined. In Table V the results are contrasted with those from the anaemic patients of the same weight range. The groups have virtually identical blood volumes, the anaemic group showing a reduction in cells equal to the increase in plasma.

The volumes observed in the last six men and seven women with rheumatoid disease whose anaemia proved refractory to parenteral iron therapy are shown in Fig. 8 (opposite). The outlines and mean values for the whole groups are inserted for comparison. The figures for men for all volumes were generally lower than those for the whole group; the women's results were scattered at random within the group boundaries and their mean values were slightly higher than the mean of the whole group, in proportion to the difference in average bodyweight. Neither Fig. 8 nor Table V gave any indication of the dilution of a normal volume of cells by an increased volume of plasma.

Discussion

The Evans blue method of estimation of plasma volume has been criticized, but it gives results which agree with those obtained by methods employing human serum albumin tagged with radio-iodine (Schultz, Hammarsten, Heller, and Ebert, 1953; Inkley, Brooks, and Krieger, 1955) and seems therefore to offer a reasonable estimate. Values for cell and whole blood volumes obtained from the observed plasma volume and haematocrit are perhaps less accurate, because the haematocrit is influenced by the centrifugal force applied and some plasma is inevitably trapped in the red cell column. Further, the haematocrit value of blood obtained from large veins is higher than that of the circulation as a whole. However, for comparative purposes, using standard conditions of centrifuging

TABLE V

COMPARISON OF ANAEMIC AND NON-ANAEMIC FEMALE RHEUMATOID PATIENTS WEIGHING BETWEEN 50 AND 60 KG.

Group	No. of Cases	Mean Age (yrs)	Mean Body-weight (kg.)	Mean Surface Area (sq. m.)	Hb. Value (g./100 ml.)		Volume related to											
							Bodyweight (ml./kg.)						Surface Area (l./sq. m.)					
							Plasma		Cells		Blood		Plasma		Cells		Blood	
					Mean	Range	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Anaemic ..	14	47	55·0	1·56	10·6	9·0–12·1	52·6	1·93	22·4	0·98	75·0	2·62	1·85	0·07	0·79	0·04	2·64	0·09
Non-anaemic ..	18	48	54·5	1·54	13·2	12·5–15·1	49·0	2·16	25·3	1·35	74·3	3·61	1·73	0·08	0·89	0·05	2·62	0·11
Significance of Difference					..	..	0·3>*P*>0·2		0·1>*P*>0·05		—		0·3>*P*>0·2		0·1		—	

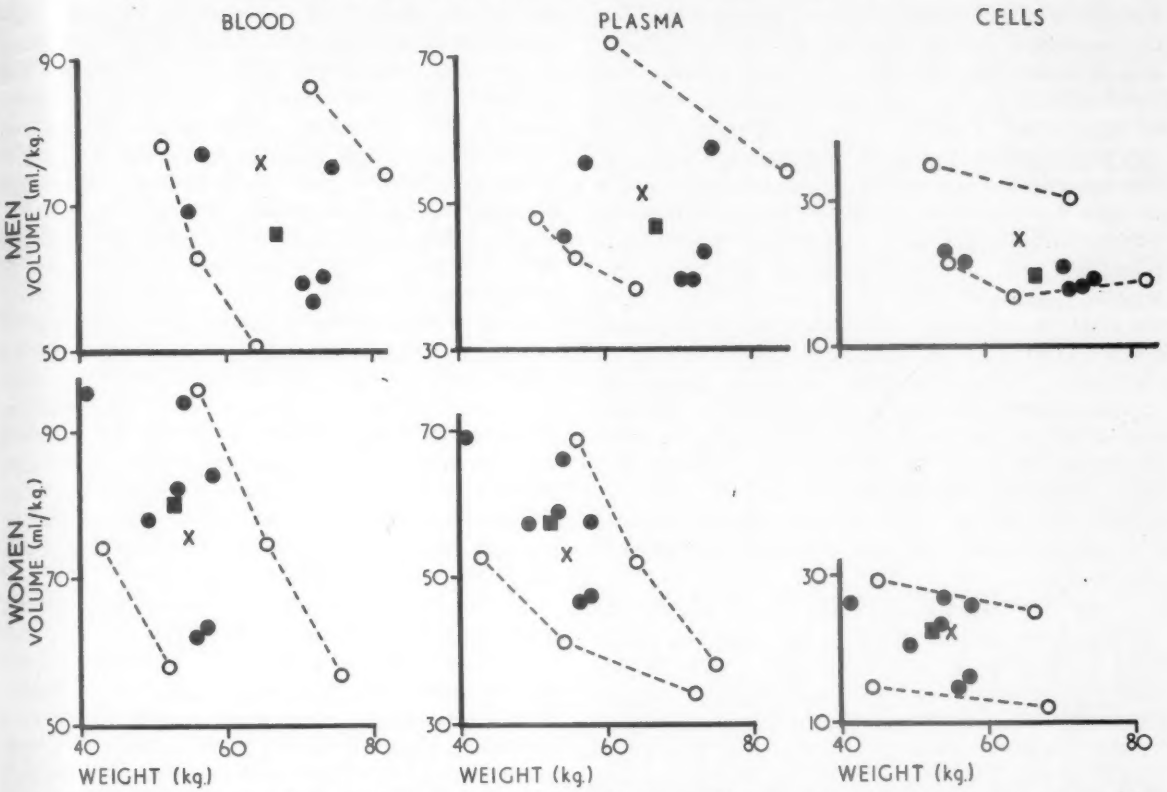


Fig. 8.—Blood, plasma, and cell volumes of six men and seven women with rheumatoid disease and anaemia refractory to parenteral iron, plotted against weight. Results shown as solid circles and mean value as a solid square. Boundaries of whole groups of rheumatoid subjects shown as open circles connected by interrupted lines. Whole group mean value shown by a cross.

etc., correction for these sources of error may be made by well authenticated factors.

Dixon and others (1955) compared simultaneous estimates of the blood volumes of normal and rheumatoid subjects by the Evans blue and ^{51}Cr-tagged red cell methods. In ten haematologically normal women, the mean value for blood volume by the dye method was 13 per cent. higher than by the tagged cell technique. It is notable that this figure of 13 per cent. was the same as that obtained by Barnes, Loutit, and Reeve (1948a), who compared estimates of blood volume obtained by the dye method and by the Ashby differential agglutination technique. Barnes, Loutit, and Reeve (1948b) did not consider that the higher figures given by the Evans blue method were explained by loss of dye from the blood stream or by any of the other obvious sources of error. It is conceivable that the dye method does, in fact, measure a slightly larger fluid compartment, plasma being able to penetrate relatively further, for example, into the interstices of sinusoids than red cells.

From the standpoint of the present investigation, the important fact is that the relation between the results from dye and tagged cell methods is the same in normal and rheumatoid subjects (Dixon and others, 1955), and comparison of our controls and rheumatoid patients by the dye method is therefore justifiable.

For any comparison of blood, plasma, or cell volumes, it is essential to refer to some measurement of bodily size, weight and surface area being the standards usually employed. Gibson and Evans (1937) analysed the relations between these volumes and bodyweight, surface area, and other factors in healthy people. They found that the blood volume tended to be higher the greater the weight, though there were wide individual variations. The relationship was not a simple "straight-line" one, for, above a moderate weight, increase in total blood volume failed to keep pace with increasing weight, so that the volume per unit weight fell. This disparity between increasing weight and blood volume was much more marked in women.

Because of these weight effects, our controls and patients were matched as nearly as possible in weight distribution. The matching was satisfactory in the men, but there was an excess of "light-weights" in

the group of rheumatoid women, the mean weights of the female groups differing by 3·5 kg. Figs 1 and 2 show that the observation of Gibson and Evans (1937), that volume per unit weight decreases as weight rises, is applicable to our subjects and that this weight effect is of considerable magnitude. If, for comparative purposes, it is assumed that a straight-line relationship obtains between blood or plasma volume per unit weight and bodyweight, regression lines may be calculated for the various groups. For both blood and plasma, the slope of the lines in the control and rheumatoid groups is quite similar and the differences could readily be fortuitous. Thus, the data, although inadequate to demonstrate that the regression lines for rheumatoid subjects and controls are the same, are perfectly consistent with this possibility. It seems very likely, therefore, that the associations of blood and plasma volumes with bodyweight in the rheumatoid patients are simply the manifestations of a general relationship.

If the results from controls and patients are combined, common regression lines may be calculated and used to determine how much of the difference between the average volumes of the control and rheumatoid groups is due to the inequality of their average weights. It emerges that the lower weight of the rheumatoid group would cause their average volumes of blood and plasma to be 3·3 and 2·5 ml./kg. higher than those of the control group. After allowing for this weight effect in the women (Table III, last row), the volume changes in male and female rheumatoid patients exhibit a common pattern, in relation both to weight and to surface area; compared with the controls, they show a marked reduction in cell volume and a smaller increase in plasma, so that the whole blood volume is somewhat reduced.

The other factor which might affect the results of volume estimations in rheumatoid disease is the presence of anaemia. The mean haemoglobin levels of our male and female rheumatoid subjects were 3·8 and 2·6 g./100 ml. below those of the controls. The volume changes in several different types of anaemia were investigated by Gibson, Harris, and Swigert (1939). These authors found a consistent pattern of changes in all the types studied, namely a reduction in red cell mass, proportional to the degree of anaemia, an increase in plasma volume, of lesser degree than the red cell reduction, and a slightly or moderately reduced blood volume.

This pattern of changes is precisely the one observed in our patients after correction for the effects of bodyweight. We conclude, therefore, that the volume changes in our patients are adequately explained by the operation of two factors of general importance, namely the effects of bodyweight and of the presence of anaemia. The slightly higher average plasma volume of the rheumatoid patients can be readily explained by their lower weight and haemoglobin levels, and there is no need to postulate a primary inflation of plasma volume.

The possibility exists that an increase of plasma occurs in patients who have very active disease or iron-refractory anaemia. Fig. 7, in which plasma volume is shown to be unrelated to the erythrocyte sedimentation rate (mm./hr; Westergren) lends no support to the first possibility. Table V, which compares groups of anaemic and non-anaemic patients of the same weight range, and Fig. 8, which displays the blood, plasma, and cell volumes of thirteen iron-refractory anaemic patients, give no evidence of dilution of a normal volume of cells by a raised plasma volume, either generally in anaemic subjects or in those refractory to iron.

It remains to consider the discrepancy between the present findings and those of Dixon and others (1955), who observed a significant increase in plasma but no significant decrease in cell volume in ten female rheumatoid patients as compared with ten controls. These authors found that the mean plasma volume of their patients was 12·8 ml./kg. higher than that of the controls, the difference in average weight being 11·3 kg.; they corrected for the weight difference by a statistical method depending on the slope of the regression line of volume upon weight. From a small number of observations, with inevitable biological variations, however, the slope of a regression line can only be determined within fairly wide limits, and our observations suggest that differences in weight have a larger effect than the slope of Dixon's line expresses. Calculation from our regression equations shows that a difference in bodyweight of 11·3 kg. would produce differences of 11·7, 8·5, and 3·2 ml./kg. in blood, plasma, and cell volumes respectively; if these corrections are used to compare rheumatoid and control groups of "equal" weight, Dixon's rheumatoid patients exhibit plasma and blood volumes which are 4·3 and 1·6 ml./kg. higher than those of the controls and a cell volume which is 2·7 ml./kg. lower. The excess of plasma over the amount needed to replace the diminished volume of cells is thus 1·6 ml./kg.; this excess might well have disappeared had further data been collected.

Summary

The blood, plasma, and cell volumes of groups of rheumatoid patients and controls have been com-

pared, using the Evans-blue-haematocrit technique.

The groups were matched as nearly as possible in terms of weight, surface area, and age.

Blood and plasma volumes were considerably affected by bodyweight, and differing weights accounted for some of the volume differences between control and rheumatoid subjects.

When the effects of weight were eliminated, the rheumatoid subjects, whose average haemoglobin level was below normal, exhibited volume changes common to many types of anaemia, namely, considerable reduction in red cell volume with a smaller increase in plasma volume, and, in consequence, some reduction in blood volume.

Patients with very active rheumatoid disease or iron-refractory anaemia did not exhibit particularly high plasma volumes.

It is concluded that the increase in plasma volume observed in rheumatoid disease is adequately explained by the operation of two general factors which influence the blood, plasma, and cell volumes, namely bodyweight and the presence of anaemia. The hypothesis of primary hydraemia, causing haemodilution, appears to be unnecessary.

My thanks are due to Drs. G. D. Kersley, J. B. Bennett, L. C. Hill, and P. W. McKeag for permission to study patients under their care. I am grateful to Dr. G. Herdan for statistical guidance and helpful criticism.

REFERENCES

Barnes, D. W. H., Loutit, J. F., and Reeve, E. B. (1948a). *Clin. Sci.*, 7, 135.
—, —, — (1948b). *Ibid.*, 7, 155.
Chaplin, H., and Mollison, P. L. (1952). *Blood*, 7, 1227.
—, —, and Vetter, H. (1953). *J. clin. Invest.*, 32, 1309.
Dixon, A. St. J., Ramcharan, S., and Ropes, M. W. (1955). *Annals of the Rheumatic Diseases*, 14, 51.
Gibson, J. G., and Evans, W. A. (1937). *J. clin. Invest.*, 16, 317.
—, Harris, A. W., and Swigert, V. W. (1939). *Ibid.*, 18, 621.
Gregersen, M. I. (1944). *J. Lab. clin. Med.*, 29, 1266.
Inkley, S. R., Brooks, L., and Krieger, H. (1955). *Ibid.*, 45, 841.
King, E. J., and Gilchrist, M. (1947). *Lancet*, 2, 201.
Robinson, G. L. (1943). *Annals of the Rheumatic Diseases*, 3, 207.
Schultz, A. L., Hammarsten, J. F., Heller, B. I., and Ebert, R. V. (1953). *J. clin. Invest.*, 32, 107.

L'hémodilution dans la maladie rhumatismale

RÉSUMÉ

A l'aide de l'hématocrite et de la méthode de Bleu d'Evans on a comparé le volume globulaire, du plasma et du sang total chez des rhumatisants et des témoins.

Les groupes furent autant que possible assortis aux points de vue poids, surface corporelle et âge.

Les volumes du sang et du plasma furent considérablement influencés par le poids du corps et les variations pondérales furent la cause de quelques unes des différences portant sur les chiffres du volume, entre les rhumatisants et les témoins.

En ne tenant aucun compte de l'influence du poids, les rhumatisants, dont le chiffre moyen d'hémoglobine était au-dessous de la normale, accusèrent des altérations de volume communes à des nombreux types d'anémie, c'est-à-dire une considérable diminution du volume globulaire accompagnée d'une plus petite augmentation du volume plasmatique et, en conséquence, d'une réduction du volume sanguin total.

Les malades atteints d'une maladie rhumatismale très active ou d'anémie réfractaire au fer n'accusèrent pas de volumes plasmatiques particulièrement élevés.

On en conclut que l'augmentation du volume plasmatique observé dans la maladie rhumatismale est convenablement expliquée par l'influence de deux facteurs généraux qui agissent sur les volumes sanguin, plasmatique et globulaire: le poids du corps et l'anémie. L'hypothèse d'hydrémie primaire causant l'hémodilution n'apparaît pas nécessaire.

La hemodilución en la enfermedad reumática

SUMARIO

Con la ayuda del hematocrito y del método de Azúl de Evans se compararon el volumen globular, plasmático y sanguíneo en sujetos reumáticos y testigos.

Ambos grupos fueron ajustados, cuanto posible, desde el punto de vista de peso, superficie del cuerpo y edad.

Los volúmenes sanguíneo y plasmático fueron considerablemente afectados por el peso del cuerpo y las variaciones ponderales fueron la causa de algunas de las diferencias respecto a las cifras del volumen, entre los reumáticos y los testigos.

Sin tener cuenta del peso, los reumáticos con cifras de hemoglobina debajo de lo normal presentaron alteraciones de volumen comunes a numerosos tipos de anemia, quere decir una diminución considerable del volumen globular con pequeña aumentación del volumen plasmático y, consecuentemente, de una reducción del volumen sanguíneo.

Los casos de enfermedad reumática muy activa o de anemia refractaria al hierro no presentaron volúmenes plasmáticos particularmente altos.

Se concluye que la aumentación del volumen plasmático observada en la enfermedad reumática se explica adecuadamente por la influencia de dos factores generales que actuan sobre los volúmenes sanguíneo, plasmático y globular: el peso del cuerpo y la anemia. La hipótesis de hidremia primaria causando la hemodilución no parece necesaria.

Ann. rheum. Dis. (1956), **15**, 160.

DECLINE OF ACUTE RHEUMATISM*

BY

R. A. N. HITCHENS

Cardiff

(RECEIVED FOR PUBLICATION APRIL 17, 1956)

The purpose of this communication is to present the statistics of acute rheumatism in school children as they have appeared in the records of the local rheumatism service in one large city (Cardiff) during the 20-year period 1931-50. The particular circumstance which gives point to the study is the well-known change which community experience of the disease has undergone in recent times: a progressive fall in mortality at ages 5-15 in England and Wales, and a reduction in the clinical severity of the acute manifestations.

Glover (1946) described rheumatic fever as an obsolescent disease as far back as the early 1930s and has referred subsequently (Glover, 1952) to the remarkable fall in mortality. For rheumatic heart disease, however, the trend of mortality has been somewhat less clear-cut. Knowelden (1949) studied mortality from rheumatic fever and heart disease in England and Wales during the years 1920-38, distinguishing separately the experience of three age groups, 5-14, 15-24, and 25-34. Rheumatic fever showed a steady decline at all ages and in both sexes, but for heart disease the trend was not uniform. In the adult age group, for men an improvement was apparent only in the early part of the period, and for women there was virtually no improvement at all. In children, the death rates declined, but the trend showed a slight setback in 1933-35 with a sharper fall thereafter.

In the context of its decline, many epidemiological features of acute rheumatism raise points of considerable interest. The association with streptococcal infection relates rheumatism to the problem of infectious diseases generally and of other streptococcal infections in particular, and the disease has a notable association with inferior living standards. Explanations of the declining mortality have been sought particularly in relation to these facts, and it is generally believed that both a change in the biology of streptococcal infection and a progressive improvement in the social condition of the population at large have contributed to the observed decline.

A number of important questions remain unanswered. What aspects of social change have been concerned in bringing about the decline in acute rheumatism? Was it, for instance, mainly due to improving material resources, to improved housing, or to better medical care? And, to consider a question of practical importance, if the country were to experience an economic depression in the near future does past experience suggest that this would be accompanied by a recrudescence of acute rheumatism? With these questions in mind the present inquiry—a retrospective study of acute rheumatism in Cardiff school children—was undertaken.

Conclusive answers cannot as a rule be expected from local inquiries, but local figures have a special importance when, as is the case with acute rheumatism, morbidity statistics on a national scale are lacking.

Source of Data and Method

The local circumstance which made the present inquiry practicable was the existence in Cardiff since 1929 of a special clinic for the observation of rheumatic children and a special hospital for "early cases of rheumatism", operated jointly by hospital consultants and medical officers of the School Health Service. Since 1931 ascertainment of rheumatic heart disease was considered to have been fairly complete, and it was especially so from 1934 onwards, when the clinic was used also for the follow-up of children discharged from the paediatric wards of local hospitals. From the beginning general practitioners were encouraged to send patients to the clinic, and cases were also referred from the education and other departments of the local authority and from the fever hospital.

Throughout the 20-year period, it was the unvarying

* This paper is an abridged version of a thesis submitted for the degree of Doctor of Medicine in the University of Wales.

policy of the school health service to refer all children suspected of rheumatism or rheumatic heart disease to the clinic; integration with the local hospitals and the co-operation of local agencies has remained a feature throughout; and it is fair to assume that the level of ascertainment in more recent years has been at least as good as it was in the early 1930s.

The clinic records dating back to 1931 were intact and included all cases under observation in that year. As it happened, the medical staff remained almost unchanged throughout, so that records were as uniform as is compatible with the medical advances which have occurred during the period. It was the custom to make a record of clinical findings on each occasion a child attended the clinic and to include a summary of progress during a stay in hospital.

Most children referred to the clinic proved to be non-rheumatic and to be suffering from postural pains, tics, and other conditions which may simulate rheumatism. Moreover, in the early years of the service, the grounds on which rheumatic fever and heart disease were diagnosed would not be acceptable by modern standards. The initial problem was therefore to make a retrospective diagnosis based on the available records of each child who had attended the clinic. This diagnosis took account only of the physical signs reported on the records; no child was considered rheumatic on the evidence of recorded history alone.

Despite the high standard of clinical recording, retrospective review was not easy. The considerable advances in methods of cardiological diagnosis and in our knowledge of the pathogenesis of acute rheumatism sometimes made the interpretation of earlier records difficult; and the criteria adopted for defining rheumatic patients had to take account of conflicting requirements:

(1) They had to be sufficiently precise for objectivity, yet elastic enough to allow for the clinical diversity of acute rheumatism.
(2) They had to be acceptable in the light of modern views, yet suitable for the categorization of cases over a 20-year period.
(3) They had to have regard for advances in diagnostic techniques, and yet they had to be applied uniformly.
(4) Due weight had to be given to the opinion of examining physicians, yet cases diagnosed on inadequate grounds had to be excluded.

These requirements are not wholly reconcilable and a compromise had to be reached, which admitted certain defects in method. There was a subjective element in assessment; the criteria employed would not satisfy a stringent modern diagnostic standard; the categorization of more recent cases took account of radiological and other special findings, while that of earlier cases was usually made on clinical grounds alone.

One circumstance partly compensated for these drawbacks. The great majority of cases were under observation for at least one year, so that the final assessment was usually made not on the results of a single examination or of a short stay in hospital, but after a substantial period of observation.

Commonly, two types of case were referred to the Rheumatism Service: those with suspected active manifestations of acute rheumatism, and those thought to have established heart disease. Separate criteria were required for these two phases of the rheumatic process.

In this retrospective survey to determine which patients had acute rheumatic manifestations, the criteria, adopted with certain modifications, were those laid down for the M.R.C. Cortisone/Aspirin Trial (M.R.C. and Nuffield Foundation, 1954, 1955), which in turn had been adapted from the classification of Duckett Jones (1944). Rheumatic manifestations were divided into major and minor types; the major included carditis, polyarthritis, chorea, nodules, and erythema marginatum, and the minor included fever, a raised erythrocyte sedimentation rate, previous streptococcal infection within one month of the rheumatic attack, a history of rheumatic fever, and (where an E.C.G. had been done) a prolonged P-R interval. A diagnosis of acute rheumatism was considered to have been established by the presence of two major manifestations or one major and two minor.

Rigid adherence to criteria designed primarily for a clinical inquiry proved, however, to be impracticable, and modifications had to be introduced. Children were sometimes first seen in the late stage of an acute episode when signs of acute carditis remained but other manifestations had subsided. Provided the signs of carditis were unequivocal, such cases were included in the rheumatic category.

In the absence of clear cardiac involvement, it proved difficult to distinguish rheumatic pains from conditions simulating them and probably this form of rheumatism was underestimated in the review. Chorea in its florid form was more readily categorized.

Criteria for those with established heart disease had necessarily to be mainly clinical in character, though, where special investigation had been carried out, these results were taken into account. Except for the post-war years, however, cardiac involvement, both acute and chronic, had usually been diagnosed on clinical grounds alone.

For this particular series of cases, cardiac murmurs proved in practice to be the most important criteria. The main problem of interpretation centred in the loud apical systolic murmur without other abnormal signs. In the early period of established heart disease following an acute rheumatic episode this is often the only abnormal sign; and in the presence of a rheumatic history it was accepted for inclusion in the category of rheumatic heart disease. In the absence of a rheumatic history, interpretation is difficult. Sometimes observation revealed acute rheumatic manifestations or changes characteristic of mitral valve involvement. There remained, however, a small group of cases in which the systolic murmur was the only evidence of heart disease throughout, and the only practicable solution was to follow the opinion of the examining physician. Cases in which any doubt as to rheumatic pathology had arisen were excluded from the rheumatic groups.

Having differentiated the rheumatic patients by these criteria, two separate rheumatism groups were dis-

tinguished, according to whether cardiac involvement was observed or not:

(1) Acute rheumatism with carditis, and patients with rheumatic heart disease.
(2) Acute rheumatism without definite heart disease.

The groups are not wholly comparable. The first provides the basis of a best available estimate of actual levels of morbidity during the period under review: ascertainment appeared to have been fairly complete; cases not recognized as such in the acute phase could often be included later; and the retrospective review was not too rigorous to be compatible with reasonable precision. The second group does not purport to represent the true amount of acute rheumatism without definite cardiac involvement: ascertainment was much less complete; cases unless seen in an acute episode could not be included later; and a precise retrospective assessment of rheumatic polyarthritis proved impracticable. Analysis and arguments are therefore based primarily on the characteristics of the Group I cases, data from the second group being used only for comparison and support.

Apart from categorization it was necessary also to estimate the date of onset. Although cases were not admitted to a rheumatism category on the basis of history alone, the history was of course accepted for dating the onset of the disease. Thus the accepted date of onset for a child first seen in 1933 with chorea and having a history of a similar attack in 1931 would be 1931.

A general reservation must be made regarding these estimates because an acute episode may have been preceded by sub-clinical rheumatism. Further, even in children, a patient with established rheumatic heart disease not infrequently has no rheumatic history, and in computing morbidity indices it was necessary to adopt a convention for this type of case.

Indices of Incidence.—In calculating incidence—*i.e.* the number of persons suffering from these diseases for the first time in any year, per 1,000 of the population at risk, or in current terminology "inception rates (persons)"—the number of persons becoming ill in any given year is counted. Alternative indices are obtained according as cases with an indefinite date of onset first coming under observation in the given year are or are not included. Both methods have been used.

These numbers when related to the mid-year school populations gave relatively rough absolute measures of sickness. For a school population, though composed predominantly of children aged 5 to 15 (5-14 before 1947), includes a proportion above this age attending grammar schools and a smaller number below 5 attending nursery schools and classes. Anomalies apply also to the age distribution of cases; in about 6·5 per cent. the illness began before the age of 5, probably before the patients had started school; and the age distribution shows a tailing off at ages 12+.

These defects detract from the value of our indices as absolute measures of sickness, but their value for comparative purposes is less affected, since similar anomalies apply to each annual rate.

Indices of Prevalence.—Prevalence rates (persons)—*i.e.* the number of persons suffering from a disease in a given year (including those whose illness started in an earlier year) per 1,000 of the population at risk—have a somewhat more restricted meaning in the present context, since they are based only on the number of persons *under observation* in any given year (including those whose illness began in an earlier year). It was remarkable how frequently patients once referred to the clinic continued under observation until they left school, with only an occasional defaulter. Nevertheless, this index—"observational prevalence"—is a low estimate of the true prevalence.

The population at risk to which these numbers ought to be related is the total number of children attending school during the same year, but this figure is unobtainable. As in the case of inception rates, the mid-year school population is used, a fact which tends to overestimate the prevalence. To what extent these two opposing tendencies counteract one another cannot be ascertained.

A more fundamental consideration relates to the natural history of rheumatic carditis. Not infrequently signs of carditis subside, and in some cases the heart becomes clinically normal. In relation to prevalence, therefore, the question arises whether patients should form the basis of rates only while abnormal signs remain or whether they should be included throughout the period of observation once abnormal signs have developed.

On clinical grounds a case could be made out for either alternative. From a statistical standpoint, the first is so difficult technically and of such limited advantage that the latter procedure was adopted.

Preliminary Analysis

It proved impracticable to obtain data from outside sources which would enable such questions as the completeness of ascertainment of rheumatic cases to be studied. No objective external evidence can be presented. This section is concerned with internal analyses bearing on the validity of the data, and with certain aspects of rheumatic cases with cardiac involvement—the main group for the present purpose.

Table I (opposite) shows the result of the review of the clinic records. The categories are mutually exclusive.

Cases with a known or suspected dual patholo (Table II, opposite) were classified as follows:

(*a*) A definite diagnosis was preferred to a doubtful one;
(*b*) Definite rheumatic carditis was preferred to other diagnoses.

Categories 3 to 8 are of importance in the present context only in so far as they enabled tests to be

TABLE I

CASES ATTENDING 1931–53, BY DIAGNOSTIC CATEGORY

	Category	Boys	Girls	Total
†1	Acute Rheumatism with Carditis ..	208	304	512
2	Acute Rheumatism without Carditis ..	110	285	395
3	Possible Acute Rheumatism with or without possible Carditis	56	94	150
4	Rheumatoid Arthritis	5	5	10
*5	Congenital Heart Disease	45	57	102
*6	Possible Congenital Heart Disease ..	6	16	22
7	Heart Disease of undetermined aetiology	14	2	16
8	Possible Heart Disease of undetermined aetiology	6	6	12
9	Other cases—a one in five sample ..	485	714	1,199

* Not an indication of incidence. Cases of congenital heart disease were supervised at the clinic only in recent years.

† Because this total includes cases attending up to 1953, it is greater than those in Tables V and VI.

TABLE II

CLASSIFICATION OF CASES WITH KNOWN OR SUSPECTED DUAL PATHOLOGY

Diagnosis	Classification	Boys	Girls
Rheumatic Carditis superimposed on Congenital Lesion	Rheumatic Carditis	—	2
Rheumatic Carditis superimposed on possible Congenital Lesion	Rheumatic Carditis	2	1
Subacute Bacterial Endocarditis superimposed on Rheumatic Carditis	Rheumatic Carditis	—	1
Rheumatoid Arthritis with Rheumatic Carditis	Rheumatic Carditis	2	—
Rheumatoid Arthritis with possible Cardiac Involvement	Rheumatoid Arthritis	4	—
Possible Rheumatism superimposed on Congenital Heart Lesion	Congenital Heart Disease	2	3
Total		10	7

made to determine if over the period there was a "transfer" of cases from one diagnostic category to another. For instance, a relative increase latterly in the size of Category 4 might have suggested a tendency for diagnosis to become more circumspect. In fact, no such evidence of a substantial "transfer" was found.

The 1,199 cases in Category 9 represent a 1 in 5 sample of by far the largest group—those which could not be assigned to Categories 1 to 8. A measure is thus provided of the ascertainment during the period of conditions which simulated rheumatism—predominantly postural pains, nervous tics, and minor anomalies of heart sounds. Because the clinic records included cards made out for persistent defaulters, the category provides also a measure of the children who failed to attend the clinic after referral.

Only 46 records out of 1,199 related to defaulters, showing that about five times this number—some 230 children—failed to attend the clinic after referral. The reason for referral was usually noted and in most cases did not suggest serious rheumatic disease. If the defaulting group contained the same proportion of true acute rheumatism and heart disease as was found in children actually examined, then Categories 1 and 2 together are not deficient from this circumstance by more than about thirty cases. Distribution by year of referral does not differ materially from that by year of entering supervision.

Table III, based only on patients whose illness began in 1931-50, shows the age-sex distribution at

TABLE III

CASES WITH ONSET IN 1931–50, BY SEX AND AGE AT ONSET

Age at Onset (yrs)	Acute Rheumatism with Carditis (Category 1)		Acute Rheumatism without definite Carditis (Category 2)		Doubtful Rheumatism (Category 3)		No Definite Evidence of Rheumatism (Category 9)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Under 3	—	—	—	—	—	—	8	7
3—	5	8	1	—	3	4	8	13
4—	12	7	3	7	5	7	24	25
5—	6	24	4	12	5	6	36	44
6—	14	17	12	13	7	9	37	49
7—	24	22	14	30	4	8	35	46
8—	21	20	11	28	6	5	43	48
9—	14	34	7	38	7	15	37	84
10—	21	29	12	36	2	8	30	61
11—	14	15	8	28	3	9	25	57
12—	7	13	8	27	4	6	21	49
13—	6	6	10	21	1	1	4	31
14—	3	2	1	2	—	—	3	4
15+	1	1	—	3	—	—	—	1
Totals	148	198	91	245	60	94	322	519
Age not Assessable ..	19	42	—	5	13	13	85	78
Mean	8·8±0·22	8·7±0·18	9·3±0·27	9·8±0·16	7·9±0·35	8·4±0·27	8·3±0·16	9·1±0·11
S.D.	2·7	2·5	2·6	2·5	2·7	2·6	2·8	2·6

onset for Categories 1, 2, 3, and 9. Apart from Category 2, all show a tailing off at the older ages. In each category, girls are markedly in excess, particularly in Category 2 which is due to the heavy weighting with chorea.

For Category 9, representing the largest section of the clinic population, girls were in excess throughout the period, but for the groups of true rheumatism the sex ratio fluctuated curiously (Table IV).

Among cases with heart disease, girls were in excess in 1931-35 and 1941-45, but not in the other two quinquennia. Among cases without definite heart disease, the excess of girls was most marked in 1936-40. No administrative circumstance could be found which might have biased sex representation during the period.

Since the trend is not uniform, the changing sex ratio is difficult to interpret. It will be recalled that individual surveys have shown variations of the sex ratio in regard to acute rheumatism ranging for instance from two boys to three girls in Belfast (Stevenson and Cheeseman, 1953) to less than four boys to five girls in the notification areas in England and Wales (Conybeare, 1951). If there are regional variations, temporal changes in the experience of one community might not be unexpected.

Turning to certain clinical aspects of the rheumatic carditis group, Table V shows the condition of the heart on entry into observation, distinguishing duration of history; 81 per cent. of those seen within one year of apparent onset and 94 per cent. of those seen later showed definite signs of carditis from the start.

Table VI (opposite) shows the cardiac condition at the end of the period of observation, distinguishing rheumatic activity on first attendance. In a substantial proportion, the signs of carditis were modified or had disappeared by the end of supervision. The larger proportion showing cardiac damage at the end, which is seen in the group who were non-active when first observed, is a consequence of the method used in the present inquiry. Since only *observed* signs of rheumatic disease qualified for classification in the rheumatic groups, cases entering observation with a history of rheumatism were included only if they presented signs. In a high proportion of these, permanent cardiac damage was already present when first seen.

There is also an interesting sex difference. For both groups of cases, signs of permanent cardiac damage were more frequent in girls than in boys. For the total of all cases and for those seen initially in an acute stage, the differences are significant at the customary level ($9{\cdot}5 \pm 3{\cdot}9$ per cent. and $13{\cdot}0 \pm 6{\cdot}2$ per cent. respectively).

Two implications of these findings must be mentioned:

(*i*) Because cases in Category 1 did not necessarily display signs of heart disease throughout the period

TABLE IV

CATEGORY 1, CATEGORY 2, AND CATEGORY 9. SEX RATIOS (BOYS AS PERCENTAGE OF TOTAL) ACCORDING TO QUINQUENNIUM OF ONSET WHERE ASSESSABLE, AND OF ASCERTAINMENT, 1931–50

Quinquennium		1931–35	1936–40	1941–45	1946–50
of Onset (where assessable)	Category 9	39	38	36	39
	Category 1	37	51	40	51
	Category 2	28	17	29	42
of Ascertainment	Category 9	41	38	41	41
	Category 1	35	49	40	48
	Category 2	29	17	28	41

TABLE V

CASES WITH RHEUMATIC CARDITIS UNDER OBSERVATION 1931–50: CONDITION OF HEART ON ENTRY INTO OBSERVATION, BY SEX

Cases Seen	Cardiac Signs	Boys	Girls	Total
Within one year of apparent onset	Nil abnormal	15	6	21
	Doubtful significance ..	9	25	34
	Definite Carditis	93 (79·5%)	135 (81·3%)	228 (80·6%)
		117	166	283
One year or more after apparent onset	Nil abnormal	—	2	2
	Doubtful significance ..	5	7	12
	Definite Carditis	83 (94·3%)	121 (93·1%)	204 (93·6%)
		88	130	218

TABLE VI

CASES WITH RHEUMATIC CARDITIS: CONDITION OF HEART AT END OF OBSERVATION PERIOD ACCORDING TO ACTIVITY OF RHEUMATIC PROCESS AT FIRST ATTENDANCE, BY SEX

Sex	Activity of Rheumatism on First Attendance	Cases under Observation up to 1950	Average Duration of Supervision	Signs of Chronic Carditis		Equivocal Signs	No Apparent Abnormality
				No.	Per cent.		
Boys	Acute	104	4·1	58	55·8	19	27
	Not acute	101	3·2	88	87·1	10	3
Girls	Acute	144	4·0	99	68·8	19	26
	Not acute	152	3·0	140	92·1	9	3
Persons	Acute	248	4·0	157	63·3	38	53
	Not acute	253	3·1	228	90·1	19	6

of supervision, criteria for the computation of observational prevalence rates are placed in doubt (see above). In fact, the definition adopted was the number of cases under observation in a given year who had at any time shown signs of carditis as a ratio of the population at risk.

(*ii*) This implication has a bearing on the completeness of ascertainment. Signs of carditis may disappear completely when an acute rheumatic episode subsides. In this inquiry, if such a case were seen in the acute stage, the patient was included in Category 1. If the case were seen afterwards when the signs had subsided, the patient could only be so included if there were a recurrent episode or if signs of established heart disease appeared later. It follows that earlier referral leads to a more complete assessment in an inquiry of this kind.

A classification of the records in four quinquennia according to length of history before ascertainment shows that as the years went by a rising proportion of patients were seen within one year of onset. Hypothetically, this might be attributable to a falling off in case-finding of established heart disease in the later years. There may possibly have been such a falling off during the war years, but taking the period as a whole it is much more likely that ascertainment became steadily more complete. To the extent that this is so, the actual decline in rheumatic heart disease will be understated by the indices employed.

Statistical Findings

Broadly the analyses it is proposed to introduce under this heading bring out two main facts:

(1) There was a substantial decline in the incidence of acute rheumatism and rheumatic heart disease during the 20-year period. The fall was most rapid during the 1930s.

(2) The trend in rheumatism differs from the apparent trend in the large group of non-rheumatic conditions which came to the notice of the clinic. Distortion of the rheumatic trend by administrative circumstances is therefore unlikely.

The trend is discussed in the context of relevant epidemiological facts.

Prevalence and Inception.—Table VII shows the observational prevalence of rheumatic heart disease among Cardiff school children during the 20-year period. The prevalence reached an apparent peak in 1934-36, and declined steadily and substantially until 1944, after which it remained relatively stationary until 1950. The rate by the end of the period was less than one half the level during the peak year. The apparent rise to a peak in 1934 is probably an artefact, since the Rheumatism Service came into operation only in 1929 and case-finding was not at first fully effective. From the end of 1933

TABLE VII

ACUTE RHEUMATISM WITH HEART DISEASE. ANNUAL OBSERVATIONAL PREVALENCE RATES, 1931–50

Year	Cases under Observation			Annual Prevalence Rates per 1,000 School Population
	Boys	Girls	Total	
1931	51	78	129	3·35
1932	53	108	161	4·14
1933	59	115	174	4·37
1934	69	124	193	5·08
1935	74	125	199	5·19
1936	78	112	190	5·24
1937	75	93	168	4·72
1938	74	88	162	4·64
1939	63	73	136	3·98
1940	52	56	108	3·23
1941	44	48	92	3·56
1942	39	45	84	2·76
1943	36	41	77	2·51
1944	34	40	74	2·38
1945	32	47	79	2·49
1946	35	43	77	2·45
1947	35	42	77	2·40
1948	39	37	76	2·25
1949	37	39	76	2·23
1950	36	43	79	2·27

onwards, consultant supervision became a feature of the Rheumatism Service. At the time this meant a modification of the diagnostic categories employed, which must in some measure have been reflected in the statistics now presented despite retrospective review. There are certain clear-cut features, however, which are unlikely to have been falsified by this circumstance.

The annual inception rates for rheumatism are shown in Table VIII, together with the annual apparent inception rates for cases in the non-rheumatic category. There is an interesting contrast between the trend for the rheumatic groups on the one hand and that for the non-rheumatic conditions on the other.

Considering first the trend in incidence of rheumatic heart disease, three features are noteworthy:

(*i*) The striking decline; by 1950 the inception rate was only one-third of the level of that in the early 1930s.

(*ii*) Both measures of incidence show that the fall was most marked in the earlier part of the period.

(*iii*) This feature is shown clearly only by incidence rate (*a*). The year 1935 appeared to mark a turning point; incidence which had remained at a high level, though fluctuating widely during the preceding 4 years, fell abruptly by one-half and never regained its former high level. It is significant that this feature is obscured in incidence rate (*b*) by the relatively large number of cases with insidious onset entering observation in 1935 and 1936. These almost certainly mainly represent children who acquired their rheumatic disease with little or no overt clinical disturbance during the period of high incidence up to 1934.

The main features of the incidence of acute rheumatism without definite carditis are strikingly similar, having regard for the known deficiencies of ascertainment in this group. The overall decline, though not so marked, was continuous and again the rate of fall was greatest in the earlier years. Furthermore, as with rheumatic heart disease, a sharp fall was recorded in 1935.

The trend in the apparent incidence of cases regarded as non-rheumatic differs. There was a substantial decline taking the period as a whole, but this was less marked in the 1930s than subsequently; the peak year of inception was not reached until 1936; and it was only after 1938 that there was an unmistakable fall. The factors responsible for this fall—chiefly a decline in the

TABLE VIII

ACUTE RHEUMATISM WITH CARDITIS (CATEGORY 1) AND WITHOUT DEFINITE CARDITIS (CATEGORY 2). ANNUAL INCEPTION RATES (*a*) AND (*b*) COMPARED WITH INDEX OF APPARENT ANNUAL INCEPTION RATES (*a*) AND (*b*) OF CONDITIONS SIMULATING ACUTE RHEUMATISM (CATEGORY 9), 1931–50

Year	Acute Rheumatism with Carditis (Category 1)				Acute Rheumatism without Carditis (Category 2)				No Definite Evidence of Rheumatism (Category 9)			
	(*a*)		(*b*)		(*a*)		(*b*)		(*a*)		(*b*)	
	Annual Inception Rate per 1,000	Average Rate in Quinquennium	Annual Inception Rate per 1,000	Average Rate in Quinquennium	Annual Inception Rate per 1,000	Average Rate in Quinquennium	Annual Inception Rate per 1,000	Average Rate in Quinquennium	Annual Inception Rate per 1,000	Average Rate in Quinquennium	Annual Inception Rate per 1,000	Average Rate in Quinquennium
1931	0·83		1·01		0·91		0·93		1·79		1·95	
1932	1·31		1·42		0·80		0·80		1·44		1·60	
1933	0·60	0·86	0·73	1·04	0·58	0·73	0·60	0·74	1·81	1·68	1·99	1·91
1934	1·02		1·21		0·95		0·95		1·68		1·89	
1935	0·55		0·81		0·42		0·44		1·67		2·14	
1936	0·58		0·83		0·41		0·44		2·10		2·57	
1937	0·45		0·59		0·37		0·37		1·66		2·08	
1938	0·54	0·44	0·60	0·54	0·54	0·49	0·54	0·50	1·49	1·46	1·80	1·78
1939	0·35		0·38		0·56		0·59		1·17		2·26	
1940	0·30		0·30		0·57		0·57		0·90		1·17	
1941	0·39		0·43		0·43		0·43		1·32		1·59	
1942	0·26		0·33		0·13		0·13		1·15		1·45	
1943	0·36	0·35	0·39	0·37	0·42	0·36	0·42	0·36	1·21	1·05	1·37	1·28
1944	0·22		0·22		0·52		0·52		0·71		1·00	
1945	0·50		0·50		0·32		0·32		0·88		0·98	
1946	0·19		0·22		0·41		0·41		0·75		1·00	
1947	0·37		0·44		0·34		0·34		0·81		1·15	
1948	0·30	0·29	0·33	0·34	0·36	0·34	0·36	0·34	0·44	0·62	0·50	0·80
1949	0·32		0·32		0·38		0·38		0·65		0·76	
1950	0·29		0·37		0·20		0·20		0·46		0·60	

(*a*) Based on cases with known onset in a given year.
(*b*) Based on cases with known onset plus those with unspecified onset first entering observation in a given year.

incidence of postural pains, and, with advancing knowledge, increasing selectivity in the type of case referred—produced an apparent trend quite different from that observed in acute rheumatism.

The differing apparent trend of non-rheumatic cases—based on patients comprising the great majority of referrals to the clinic—suggests that there was no serious distortion of the rheumatic trend through administrative circumstances.

The observed incidence of rheumatic heart disease in the years 1948-50 did not much differ from the rates reported from notification areas in other parts of England and Wales. In 1948, for instance, the inception rate in Cardiff was 0·30 per 1,000 children compared with 0·26 per 1,000 in the notification areas. This supports the view that the ascertainment in Cardiff in later years was fairly satisfactory.

Epidemiological Comparisons.—There is obvious interest in comparing the observed trend of rheumatism with the trends in other streptococcal illnesses on the one hand and with socio-economic tendencies on the other.

The first comparison is with the trend in notification figures for scarlet fever in the city, the only useful data relating to streptococcal illness. The abrupt fall in the incidence of rheumatism in 1935 after a period of relatively heavy morbidity suggests the operation of a single factor and focuses attention on the possibility of a contemporaneous change in some characteristic of the streptococcus or its distribution.

The notification figures for scarlet fever (Table IX) appear at first sight to support this view. Notifications, which had been exceptionally heavy from 1931 to 1934, dropped sharply in 1935. But the significance of this finding becomes less clear when the figures are compared with those for rheumatism over the whole period. At no stage was there a consistent relationship. Further, whereas from 1931 to 1934 scarlet fever was epidemic in Cardiff, there is no reason to suppose that the incidence of acute rheumatism was substantially greater than before 1931.

An equally interesting comparison is with the trend in the severity of scarlet fever. Here it is necessary to turn to national statistics. Annual mortality and case fatality rates for England and Wales are shown in Table X. Once more the isolated fact emerges that 1935 was a year of change. Since 1912 deaths had fallen steadily to reach by 1927 a figure in the 500s. During the next 7 years, when scarlet fever notifications increased, there were fluctuations with a substantial rise in mortality during 1933 and 1934. In 1935, however, mortality returned to its former level and from then onwards an annual decline in the number of deaths has continued almost without interruption. Similarly, case fatality rates, which had declined steadily from 1911 onwards, remained relatively stationary from

TABLE IX

ACUTE RHEUMATISM WITH AND WITHOUT CARDITIS. ANNUAL PERCENTAGE CHANGE IN INCEPTION RATE(*a*) COMPARED WITH ANNUAL PERCENTAGE CHANGE IN THE NUMBERS OF CASES OF SCARLET FEVER NOTIFIED (CARDIFF, 1931–50)

Year	Scarlet Fever		Acute Rheumatism with Carditis		Acute Rheumatism without Carditis	
	Cases Notified	Annual per cent. Change	Inception Rate(*a*)	Annual per cent. Change	Inception Rate(*a*)	Annual per cent. Change
1931	632		0·83		0·91	
1932	726	+15	1·31	+58	0·82	−10
1933	1308	+80	0·60	−54	0·58	−29
1934	905	−31	1·02	+70	0·95	+64
1935	378	−58	0·55	−53	0·42	−56
1936	361	− 5	0·58	+ 5	0·44	+ 5
1937	495	+37	0·45	−22	0·39	−11
1938	841	+70	0·54	+20	0·57	+46
1939	786	− 7	0·35	−35	0·59	+ 4
1940	293	−63	0·30	−15	0·57	− 3
1941	184	−37	0·39	+30	0·43	−25
1942	318	+73	0·26	−33	0·16	−63
1943	590	+86	0·36	+38	0·42	+162
1944	602	+ 2	0·22	−39	0·52	+24
1945	309	−49	0·50	+127	0·32	−38
1946	331	+ 7	0·19	−62	0·47	+47
1947	434	+31	0·37	+95	0·34	−28
1948	595	+37	0·30	−19	0·36	+ 6
1949	301	−49	0·32	+ 7	0·41	+14
1950	289	− 4	0·29	− 9	0·20	−51

TABLE X

SCARLET FEVER. ANNUAL NUMBER OF NOTIFICATIONS. DEATHS AND CASE FATALITY RATES, ENGLAND AND WALES, 1911–50

Quinquennium or Year	Notifications	Deaths	Fatality Rate (per 100 cases)
1911–15	634,543	11,236	1·8
1916–20	374,607	5,820	1·6
1921–25	506,934	5,556	1·1
1926	81,672	677	0·83
1927	84,450	579	0·68
1928	102,611	580	0·57
1929	120,232	717	0·60
1930	111,077	740	0·67
1931	81,569	540	0·66
1932	84,982	530	0·62
1933	129,436	729	0·56
1934	151,867	963	0·63
1935	120,317	573	0·48
1936	104,710	495	0·47
1937	95,569	349	0·37
1938	98,815	311	0·31
1939	77,591	181	0·23
1940	63,804	152	0·24
1941	58,072	131	0·23
1942	83,847	100	0·12
1943	113,931	129	0·11
1944	90,616	105	0·12
1945	72,187	82	0·11
1946	56,124	41	0·07
1947	57,264	42	0·07
1948	73,947	37	0·05
1949	70,207	18	0·03
1950	65,889	33	0·05

1928 to 1934, but in 1935 the decline was resumed. These relationships in 1935 may or may not have been coincidental; no final conclusions are possible from the present data.

The next comparison is with local figures of unemployment and recourse to poor relief (Table XI). It is well known that Cardiff, in common with other "depressed areas" was late in registering an improvement. No real advance was, in fact, made until 1937, but it is noteworthy that the incidence of rheumatism in the city had fallen 2 years before this improvement was registered.

TABLE XI

UNEMPLOYMENT OF MALES AGED 18–65 (1931–40) AND POOR RELIEF (ANNUAL RATE, 1931–39)

Year	Men on Unemployment Register (at Mid-year)	Unemployment Rate per 1,000 Males	Poor Relief Annual Rate (at Mid-year) per 10,000 estimated population (including dependants)
1931	14,579	234	378
1932	15,115	244	431
1933	15,870	257	505
1934	14,909	243	530
1935	14,338	242	503
1936	13,320	216	508
1937	10,540	172	442
1938	9,793	158	431
1939	7,438	119	416
1940	3,892	62	—

Other social improvements which occurred during the 1930s are not easily expressed in numerical terms. Housing programmes, relief of overcrowding, and improved welfare services for mothers and children were all measures which might theoretically have influenced the rate of occurrence of the disease. Such benefits were not, however, on a scale or of a kind which might have been expected to produce a relatively dramatic fall in the incidence of rheumatism, and many were hardly begun in the first half of the decennium, and although advances were taking place in Cardiff during the 1930s, it is difficult to believe that they played a major role in the decline of the disease at the time.

Finally, chemotherapeutic agents came into increasing, and subsequently, widespread use from the late 1930s onwards; they may well have contributed latterly to the decline in rheumatism, but it is clear that they were not among the principal causes of the decline.

Social Differentials.—In an effort to study the problem further, rheumatic cases were classified according to a social grouping. Recording of father's occupation was insufficiently precise to enable cases to be allocated to the Registrar-General's social class grouping. The only available methods of studying social differentials were by reference to schools attended and to the Wards of the City in which patients resided. Both methods gave similar results and the former is now briefly described (grammar schools and special schools excluded).

Schools were grouped on a simple four-point social scale:

I. Predominantly working class.
II. Predominantly working class (new housing estates).
III. Mixed working and middle class.
IV. Predominantly middle class.

Ascertainment rates of the two designated forms of rheumatism (defined as the average annual number of cases ascertained per 1,000 of the average annual school population) were then computed for each group in the two decennia 1931-40 and 1941-50 (Table XII). In the first decennium the rate for carditis in the middle-class schools was significantly lower than the rates for the other three groups, Group I being slightly in excess. In the second decennium a gradient remained, though the gap between the middle-class schools and the other schools was somewhat narrower. The percentage decline was very similar for Groups I to III.

TABLE XII

ACUTE RHEUMATISM WITH AND WITHOUT DEFINITE CARDITIS. COMPARISON OF ASCERTAINMENT RATES ACCORDING TO TYPE OF SCHOOL ATTENDED,* 1931-50

Acute Rheumatism	School Group	I	II	III	IV
With Carditis	Cases ascertained 1931–40	177	48	98	19
	Cases ascertained 1941–50	46	19	16	11
	Ascertainment Rate (*a*) 1931–40	1·18	0·95	1·08	0·50
	Ascertainment Rate (*b*) 1941–50	0·43	0·35	0·37	0·27
	Rate (*b*) as percentage of Rate (*a*)	36	37	34	54
Without Carditis	Cases ascertained 1931–40	118	35	69	15
	Cases ascertained 1941–50	48	21	27	9
	Ascertainment Rate (*a*) 1931–40	0·78	0·69	0·76	0·40
	Ascertainment Rate (*b*) 1941–50	0·45	0·38	0·38	0·22
	Rate (*b*) as percentage of Rate (*a*)	58	55	50	55

* Children attending grammar schools and special schools excluded.

For other forms of rheumatism there was a similar pattern. Rates for the first three groups were high compared with middle-class schools, and again Group I was the highest of the three but not significantly so. Comparing decennia, the extent of decline was about the same for all four groups.

A geographical study of the location of patients' dwellings showed little noteworthy aggregation of cases in any one part of the city. There were, however, 29 clear instances in which two or more rheumatic siblings had attended the clinic during the period considered.

The conclusions which can be reached from a relatively rough social study of this kind are limited, but three points are worthy of mention:

(1) There is a relation with socio-economic status. The occurrence of rheumatism was consistent with the view that the less well-to-do experienced a relatively high incidence. It is possibly noteworthy that there was not a straightforward social gradient, the "mixed" schools having similar rates to the predominantly working-class groups.

(2) Comparing decennia, for rheumatic heart disease, the social differential was somewhat less marked in 1941-50, but for other forms of rheumatism it remained the same. There was no dramatic change of the kind which might have been expected had incidence levels been closely related to the widespread lack of material resources which was a feature of the 1930s.

(3) Rates for children representing the experience of those living on new housing estates were rather consistently a little lower than the rates for other working-class children, but in no case was the difference significant statistically. It did not appear that residence on a new housing estate, *per se*, influenced the risk of a child acquiring rheumatism to any considerable extent.

Discussion

The years 1931-50 witnessed a remarkable change in mortality from acute rheumatism and heart disease at ages 5-15. From the beginning of the 20th century up to 1930 the death rate had been falling slowly. The decline was halted temporarily in the early 1930s to be resumed in 1936, after which date it fell continuously and more steeply than before.

The setback in 1931-35 occurred at a time of industrial depression and the resumption of the decline coincided with a return to national prosperity. The war years, though they meant a deterioration in housing and for many a disruption of ordinary home life, brought higher wages for a large section of the working population, and high wages and full employment have been so far maintained in the post-war period.

These temporal associations, taken together with the well known poverty relationship of rheumatism, suggest that the recent history of the disease might have been closely related to economic trends. This view is supported in an inquiry by Morris and Titmuss (1944), who studied mortality from rheumatism in the county boroughs of England and Wales during the 1930s, in conjunction with changes in unemployment figures. Their conclusion was that unemployment was an important factor *per se* in determining levels of mortality.

These findings cannot, however, be interpreted in isolation from the trend in total mortality at ages 5-15 over the same period. As with certain individual causes of death such as acute rheumatism, there is a general relationship between poverty and total mortality in childhood. It is therefore important to notice that the trend in total mortality in England and Wales at ages 5-15—a steady decline—was uninterrupted during the worst years of depression (Tables XIII and XIV).

TABLE XIII

AVERAGE ANNUAL DEATH RATES PER 1,000 LIVING AT AGES 0–20 BY AGE GROUPS, AND INFANT MORTALITY (1901–50), ENGLAND AND WALES

Age Group (yrs)		0–	5–	10–	15–20	Deaths under 1 year per 1,000 Live Births
Quin-quennium	1901–05	50·2	3·74	2·19	3·11	138
	1906–10	41·7	3·38	2·03	2·87	117
	1911–15	37·5	3·39	2·08	2·88	110
	1916–20	31·4	3·81	2·48	3·77	90
	1921–25	24·4	2·48	1·71	2·61	76
	1926–30	20·8	2·37	1·57	2·49	68
	1931–35	18·1	2·18	1·41	2·33	62
	1936–40	15·6	1·84	1·20	2·01	55
	1941–45	14·0	1·50	1·08	1·96	50
	1946–50	9·33	0·77	0·62	1·18	36

TABLE XIV

AVERAGE ANNUAL DEATH RATES PER 1,000 LIVING AT AGES 0–20 BY AGE GROUPS, AND INFANT MORTALITY (1906–50) EXPRESSED AS PERCENTAGES OF RATES IN 1901–05, ENGLAND AND WALES

Age Group (yrs)		0–	5–	10–	15–20	Infant Mortality
Quin-quennium	1901–05	100·0	100·0	100·0	100·0	100·0
	1906–10	83·1	90·4	92·7	92·3	84·8
	1911–15	74·7	90·6	95·0	92·6	79·7
	1916–20	62·5	101·9	113·2	121·2	65·2
	1921–25	48·6	66·3	78·1	84·0	55·1
	1926–30	41·4	63·4	31·7	80·0	49·3
	1931–35	36·1	58·3	64·4	74·9	44·9
	1936–40	31·1	49·2	54·8	64·6	39·9
	1941–45	27·9	40·1	49·3	63·0	36·2
	1946–50	18·6	20·6	28·3	37·9	26·1

Two facts in particular might be emphasized:

(*i*) Mortality from the infectious diseases which were of importance in the early part of the century and together accounted for a major part of total mortality, was falling dramatically;

(*ii*) The areas most affected by the economic slump shared in the general improvement.

The first point has an important implication. Apart from the special circumstances which can explain the decline in mortality from certain individual infectious diseases, the fact that they all declined simultaneously strongly suggests that socio-economic betterment was also an important factor. It would be stretching coincidence too far to suggest contemporaneous changes in a number of host-parasite relationships all favourable to the host.

The second point was brought to light by an inquiry described in a Report of the Chief Medical Officer to the Ministry of Health (1932). The inquiry failed to disclose any deterioration in health which could be clearly related to industrial distress and unemployment. The general death rate and infant mortality in certain representative depressed areas were higher than in the remainder of the country, but the proportionate decline in mortality in the depressed areas in the period of economic depression was actually greater than in the country as a whole. The inference drawn was this:

> . . . We cannot escape the conclusion that there is at present no available evidence of any general increase in physical impairment or in mortality as the result of economic depression or unemployment.

During the slump period housing conditions did not deteriorate, but were in fact gradually improving as local authorities developed their housing programmes. Unemployment might have been expected to have other unfortunate consequences; there was, for instance, less money for food, fuel, and clothing, and it would not have been surprising if loss of morale had resulted in a lowering of the standard of child care. In the event, although deterioration in clothing and footwear was reported, nutritional standards were well maintained so far as school children were concerned, and the incidence of lousiness—a useful rough and ready index of child care—continued to decline. The evidence suggests that for this age group the intimate environment of the home deteriorated surprisingly little.

There are many difficulties in the interpretation of these facts. For instance, the steady fall in the average size of family since the beginning of this century both facilitates a higher standard of child care and is likely to reduce the risk of infection in the home. Standards of housing, though well known to be closely related to many health problems, do not appear to have a significant bearing on the juvenile mortality trend.

An hypothesis postulating a close relationship between incidence of disease and current economic conditions places rheumatism in a special category.

This is the context in which the trend of morbidity in Cardiff is now considered. Interpretation is limited by a number of circumstances. The period under review is relatively short and nothing is known of incidence before 1931; the experience is local so that random fluctuations cannot be ruled out; the relevant epidemiological data are not complete. Our conclusions must necessarily be tentative, but three features of the trend appeared particularly significant:

(1) Comparing average annual rates in quinquennia there was a consistent decline throughout the period.
(2) The sharpest part of the fall occurred during the 1930s when economic improvement was least evident, and the decline had started 2 years before any substantial improvement in employment had been registered at all.
(3) The decline began with an abrupt fall in 1935 after a period of high, though fluctuating, incidence.

There is no support here for the view that economic conditions *per se* were an important cause of the decline. Taking all the known facts into account, the trend agrees best with the hypothesis that a sharp decline brought about by some change in the properties or distribution of the streptococcus was superimposed on a progressive fall due to steady social improvement.

The general improvement in child health during 1931-50 occurred in a manner which suggests that, in so far as they are separable, socially determined factors such as the quality of maternal care were of greater importance than either economic standards *per se*, or the physical factors customarily thought important in disease causation. Such an explanation would be consistent also with the trend of rheumatism observed in Cardiff over the period surveyed. The assessments and other information required to establish the fact, however, are not obtainable.

If the decline in rheumatism were, indeed, so determined, it would follow that an economic catastrophe, even on the scale of the industrial depression of the 1930s, would be unlikely to reverse the present trend in the disease.

Summary

(1) Local statistics of the incidence of acute rheumatism and rheumatic heart disease for the years 1931-50 were derived from a retrospective

review of the records of the Cardiff Rheumatism Service for school children.

(2) The following facts emerge from this study:

(*a*) A substantial decline occurred over the 20-year period.

(*b*) The greatest rate of decline occurred in the 1930s before there had been substantial local economic improvement.

(*c*) The decline began abruptly in 1935, coinciding perhaps fortuitously with a sharp drop in the notification figures for scarlet fever in the city and a resumption of the decline in national mortality from that disease.

(*d*) The social analysis was consistent with the view of a poverty relation. Comparing the two decennia 1931-40 and 1941-50, there was some change in the social differential of rheumatic heart disease, but none in that of other forms of acute rheumatism. Residence in a new housing estate conferred little advantage.

(3) On the basis of these local figures and more general considerations, reasons for the decline in the disease are discussed. It is suggested that social causes of the decline are related more closely to such factors as an improving quality of maternal care than to straightforward economic or physical factors. If this view is correct, the present trend of the disease is unlikely to be reversed by an economic slump.

Acknowledgements are due to the Medical Officer of Health to the City of Cardiff for access to the records; to Dr. C. W. Anderson, Deputy Medical Officer, for information concerning the organization and practice of the Rheumatism Service; and to Messrs. V. E. Bevan and Philip Williams for the information required for certain analyses. I am indebted to Professor A. G. Watkins for help with clinical aspects and to Dr. E. Lewis-Faning for help with statistical aspects of this study, and to Professor F. Grundy for guidance and criticism throughout.

REFERENCES

Conybeare, E. T. (1951). *J. roy. sanit. Inst.*, 71, 300.
Glover, J. A. (1946). *Monthly Bull. Minist. Hlth*, 5, 222.
—— (1952). *In* "History of the Second World War. Medicine and Pathology", ed. V. Zachary Cope, p. 113. H.M.S.O., London.
Jones, T. Duckett (1944). *J. Amer. med. Ass.*, 126, 481.
Knowelden, J. (1949). *Brit. J. Soc. Med.*, 3, 29.
Ministry of Health (1932). "13th Annual Report of the Ministry of Health, 1931–32." H.M.S.O., London.
Morris, J. N., and Titmuss, R. M. (1944). *Med. Offr.*, 72, 69, 77, 85.
M.R.C. and Nuffield Foundation (1954). *Brit. med. J.*, 1, 1223.
—— —— (1955). *Ibid.*, 2, 695.
Stevenson, A. C., and Cheeseman, E. A. (1953). *Ann. Eugen. (Camb.)*, 17, 177.

Le déclin du rhumatisme aigu

RÉSUMÉ

(1) Les statistiques locales de la fréquence du rhumatisme aigu et de la maladie de Bouillaud pour les annèes 1931-50 ont été établies d'après les archives du Service de Rhumatisme de Cardiff pour les écoliers.

(2) Cette étude fait apparaître les faits suivants:

(*a*) Un déclin substantiel s'est produit durant cette période de 20 ans;

(*b*) Le déclin le plus marqué est survenu après 1930, avant que se fût produit une substantielle augmentation du niveau de vie local;

(*c*) Le déclin s'amorça très abruptement en 1935, coincidant, peut-être fortuitement, avec une chute brusque du nombre des cas déclarés de scarlatine dans la ville, et avec un nouveau déclin de la mortalité due à cette maladie pour l'ensemble du pays.

(*d*) L'étude des conditions sociales confirma une relation avec le paupérisme. En comparant les deux décennaires 1931-40 et 1941-50, on constata un certain changement dans le rapport "niveau social—maladie de Bouillaud", mais non dans celui des autres formes de rhumatisme aigu. Le fait de loger dans une nouvelle cité conférait peu d'avantage.

(3) Sur la base de ces chiffres locaux et de considérations plus générales, on discute les raisons du déclin de cette maladie. Il est suggéré que les causes sociales de ce déclin seraient liées plus étroitement à des facteurs tels qu'une amélioration de la qualité des soins maternels que simplement à des facteurs èconomiques ou physiques. Si ce point de vue est correct, l'actuelle tendance de régression de cette maladie ne semble pas devoir être renversèe par une crise économique éventuelle.

Baja del reumatismo agudo

SUMARIO

(1) Las estadísticas locales de la frecuencia del reumatismo agudo y del reumatismo cardiaco para los años 1931-50 fueron establecidas según los archivos del Servicio de Reumatismo de Cardiff para los niños de escuela.

(2) Este estudio revela los hechos siguientes:

(*a*) Una baja considerable tuvo lugar durante este período de 20 años;

(*b*) La más importante baja ocurrió después de 1930, antes de manifestarse una aumentación substancial del nivel de vida local;

(*c*) La baja empezó muy abruptamente en 1935, coincidiendo, quizas fortuitamente, con una caída repentina del número de los casos declarados de escarlatina en la ciudad y con la continuación de la baja de la mortalidad debida a esta enfermedad en el país entero.

(*d*) El estudio de las condiciones sociales confirma una relación con la pobreza. Al comparar los dos decenios 1931-40 y 1941-50, se nota un cierto cambio en la relación "nivel social—reumatismo cardiaco" pero ninguno en las demás formas del reumatismo agudo. El hecho de vivir en casas municipales nuevas otorgó poca ventaja.

(3) A base de estas cifras locales y de cosideraciones generales se discuten las razones de la baja de esta enfermedad. Se sugiere que las causas sociales de esta baja estarían ligadas más estrechamente a factores domésticos, tales como mejores cuidados maternos, que simplemente á factores económicos o físicos. Al ser correcto este punto de vista, la tendencia presente de regresión de esta enfermedad persistiría a pesar de una crisis económica eventual.

Ann. rheum. Dis. (1956), **15**, 173.

COMPARISON OF CORTISONE ACETATE AND A CODEINE MIXTURE AS ADJUVANT TREATMENT IN JUDET ARTHROPLASTY

BY

G. P. ARDEN

Heatherwood Orthopaedic Hospital

(RECEIVED FOR PUBLICATION FEBRUARY 27, 1956)

Experimental work by Ragan, Howes, and their associates (1949, 1950) has shown that fibrous scarring is decreased by cortisone. Hip arthroplasty may be followed by excessive fibrosis and by ectopic new bone formation which causes considerable disability. Cortisone given locally and systemically has been shown by Stinchfield (1950) to improve this condition in nylon hip arthroplasty in dogs. We have therefore investigated the use of cortisone as an adjuvant to Judet arthroplasty in man.

Selection of Cases

Eighteen patients (two bilateral=twenty hips) were selected, suffering from either degenerative changes of the hip or from rheumatoid arthritis with pain severe enough to justify operative treatment, conservative measures having failed. Cases were selected at random for treatment by cortisone or codeine by a system of numbered envelopes in series, only the hospital pharmacist knowing which patients were receiving cortisone.

The patients were admitted to the hospital one week before operation.

Treatment

Cortisone acetate was given in a pink, raspberry-flavoured mixture in mist. codeine co. which alone was used for the control series. Cortisone was started 6 days before the operation at a dosage level of 150 mg./day in three divided doses for the first 4 days, then 100 mg. in four doses for the following 8 days, 75 mg. in three doses for 8 days, and finally 50 mg. for 6 days, making a total of 23 g. cortisone acetate in 26 days.

The basic codeine mixture used for the control group contained aspirin gr. 4, phenacetin gr. 4, codeine phosphate gr. $\frac{1}{8}$, to the half ounce; it was given at the level of 1 oz. three times a day for 4 days, then $\frac{1}{2}$ oz. four times a day for 8 days, then $\frac{1}{2}$ oz. three times a day for 8 days, and finally $\frac{1}{2}$ oz. twice a day for 6 days, making a total of 11·5 gr. codeine in 26 days.

Those treating the patients did not know which cases were on codeine or cortisone (the severe oedema of legs in a patient on codeine was mistakenly attributed to cortisone).

Methods of Assessment

Pain.—This was assessed in four grades from 0-3, and measured before operation, at weekly intervals until discharge, and then at 3, 6, and 12 months.

Range of Movement in Hip.—Clinical assessments of angular movement were taken without the use of a goniometer from a position of full extension of the hip. After the operation the range of movement of the affected hip was noted weekly until discharge, and then in the out-patients department after 3 months and 6 months.

Functional Result.—This was assessed 6 months after operation on the following basis:

(*i*) *Good.*—Able to walk one mile 3 months after operation. No real pain in hip. Has returned to former occupation or activity. Uses one stick only.

(*ii*) *Fair.*—Able to walk up to half a mile. Some pain in hip. Has returned to light work or limited activity at home.

(*iii*) *Poor.*—Able to walk in house only. Considerable pain in hip. Unable to work and confined to house or bed.

TABLE I

CASE ANALYSIS

Drug	Hip No.	Age (yrs)	Sex	Diagnosis	Hip Involved	Duration of Symptoms	Signs and Symptoms			Trendelenburg's +	Use of Sticks	Domestic Difficulties		
							Pain	Stiffness	Limp			Putting on Shoes	Going Upstairs	Bathing
Cortisone	1	59	F	Rheumatoid Arthritis	L	12 yrs	7/7	2/7	3/7	4/7	4/7	6/6	0/6	2/6
	2			Rheumatoid Arthritis	R									
	3	46	F	Osteo-Arthritis	R	1 yr								
	4	75	F	Osteo-Arthritis	R	1 yr								
	6	40	M	Osteo-Arthritis	L	14 mths								
	9	61	F	Rheumatoid Arthritis	L	9 yrs								
	10	68	F	Osteo-Arthritis	R	10 yrs								
Codeine	11	62	F	Rheumatoid Arthritis	L	6 yrs	8/8	2/8	8/8	5/8	5/8	7/8	5/8	1/8
	12			Rheumatoid Arthritis	R									
	13	63	F	Rheumatoid Arthritis	L	4 yrs								
	14	64	M	Osteo-Arthritis	R	8 mths								
	16	52	M	Osteo-Arthritis	R	6 mths								
	17	60	M	Osteo-Arthritis	R	1 yr								
	18	65	M	Osteo-Arthritis	R	10 mths								
	20	72	F	Osteo-Arthritis	L	2 yrs								

Results

Of the eighteen patients taken into the trial, of whom one in each group had two hips involved, five cases had their treatment discontinued between the 8th and the 20th day of the trial on account of toxic effects (three in the cortisone group with oedema of the legs plus chest infection, plus venous thrombosis, urinary infection, and prostatic obstruction respectively, and two in the codeine group with coronary thrombosis and severe oedema of legs). This left 13 patients (15 hips) completing the trial: these two residual groups are comparable with those at the beginning of the trial (Table I).

Table II (opposite) shows that there was no real difference between the patients treated with cortisone and those treated with codeine. There was increase in movement up to 6 months, but this was not sustained in the group as a whole by the year. Pain, however, was improved, as was also the functional assessment.

Summary

(1) Two small comparable series of cases of hip disease, one treated with cortisone and the other with a codeine mixture before, during, and after a Judet arthroplasty, are discussed, and the results are compared.

(2) After 6 months and one year there was no difference between the two groups in regard to range of movement and degree of pain, and the final function was equal in both groups.

(3) No severe toxic effects were noted and there was no trouble with wound healing or wound infection.

My thanks are due to Dr. E. G. L. Bywaters for his encouragement and advice during the period of this trial and for his helpful criticisms in the preparation of this paper.

For the cortisone allocated for this trial I should like to thank the Medical Research Council and the Nuffield Foundation Joint Committee on Clinical Trials of

TABLE II

POST-OPERATIVE RESULTS

Drug	Hip No.	Pre-operative		After 3 months		After 6 months			After 12 months	
		Flexion	Pain	Post-operative Flexion	Post-operative Pain	Post-operative Flexion	Post-operative Pain	Distance Walked (mls)	Post-operative Flexion	Assessment
Cortisone	1 L	50	3	70	0	70	1	½	45	Fair
	2 R	85	2	80	0	90	1	½	60	Fair
	3	80	3	90	2	80	2	½	70	Fair
	4	80	3	80	1	100	1	100 yds	20	Fair
	6	90	3	80	1	100	0	½	90	Good
	9	30	3	75	0	70	1	1	80	Fair
	10	75	3	80	0	100	0	1	80	Good
	Average	70		78		87			63·4	
Codeine	11 L	80	3	80	3	80	2	½	80	Fair
	12 R	60	3	75	0	90	1	½	90	Fair
	13	15	3	40	0	40	0	house-bound	25	Fair
	14	40	3	90	1	100	0	3	100	Fair
	16	80	2	90	0	100	0	2	90	Good
	17	70	2	80	0	90	0	½	90	Good
	18	90	3	90	0	90	1	¾	90	Poor
	20	90	2	40	2	90	1	100 yds	30	Good
	Average	66		73		85			74	

Cortisone, ACTH, and Other Therapeutic Measures in the Chronic Rheumatic Diseases.

REFERENCES

Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **72**, 718.
——, ——, ——, ——, ——, and Lattes, R. (1950). *Bull. N.Y. Acad. Med.*, **26**, 251.
Stinchfield, F. E. (1950). *J. Bone Jt Surg.*, **32-A**, 739.

Comparaison de l'acétate de cortisone et d'une mixture de codéine comme traitement adjuvant à l'arthroplastie de Judet

RÉSUMÉ

(1) Deux petites séries semblables de cas de coxalgie l'une traitée à la cortisone et l'autre avec une mixture de codéine avant, pendant et après une arthroplastie de Judet, sont discutées et les résultats comparés.

(2) Après six mois et un an il n'y avait aucune différence entre les deux groupes en ce qui concerne l'amplitude de mouvement et l'intensité de la douleur et à la fin la fonction était égale dans les deux groupes.

(3) Aucun effet toxique sévère n'avait été constaté et il n'y avait eu aucun ennui au point de vue de la cicatrisation ou de l'infection.

Comparación del acetato de cortisona y de una mixtura de codeina como tratamineto adyuvante a la artroplastia de Judet

SUMARIO

(1) Se discuten y se comparan los resultados de dos pequeños grupos semejantes de casos de coxalgia, el uno tratado con la cortisona y el otro con una mixtura de codeina, antes, durante y después de una artroplastia de Judet.

(2) Después de seis meses y de un año no hubo diferencia alguna entre los dos grupos respecto a la amplitud del movimiento y la intensidad del dolor, y la función final fué igual en ambos grupos.

(3) No se notó ningún efecto tóxico grave y no hubo dificultades con cicatrización o con infección.

Ann. rheum. Dis. (1956), **15**, 176.

PERICARDITIS COMPLICATING RHEUMATOID ARTHRITIS

BY

A. E. THOMAS AND W. K. C. MORGAN

Royal Infirmary, Sheffield

(RECEIVED FOR PUBLICATION JANUARY 16, 1956)

The frequent occurrence of adhesive pericarditis in patients with rheumatoid arthritis has been recognized in pathological studies (Bayles, 1943; Graef, Hickey, Altman, and Rosenthal, 1948). In a study of autopsy material, Sokoloff (1953) found evidence of healed idiopathic pericarditis to be seventeen times more common among patients with rheumatoid arthritis than among other patients. Clinically, however, this condition is observed much less frequently; indeed Wood (1952) makes no reference to rheumatoid pericarditis in his textbook of cardiology.

In this communication we report three non-fatal cases of arthritis of the rheumatoid type associated with pericarditis, in two of whom L.E. cells were found in the peripheral blood.

Case Reports

Case 1, a decorator, aged 53, was admitted to hospital on 3.10.54 complaining of retrosternal pain of 4 hrs' duration. The pain, which had started suddenly, radiated to the left axilla, was accompanied by severe dyspnoea, and was intensified by breathing. Morphine sulphate gr. $\frac{1}{6}$ relieved the severe pain, but a residual retrosternal aching persisted for the next 36 hrs. In July, 1954, he had experienced a similar, but milder, attack of pain and had been treated by his own doctor for myocardial infarction.

Previous History.—At the age of 50 he had developed a progressive polyarthritis which had caused him to give up active work a few months before admission.

Examination.—He was in considerable pain, orthopnoeic, pale, sweating, and febrile (temperature 102·2° F.), blood pressure 115/80, pulse 100 and regular, apex beat in fifth left interspace 3 in. from the mid-line, heart sounds normal. Tender, soft tissue thickening of the small joints of the hands and feet with vasospasm and excessive sweating of the fingers and toes were present (Fig. 1). Typical rheumatoid nodules were visible over both elbows and there were bilateral effusions in the knees.

Fig. 1.—Radiograph of hand (Case 1) showing rheumatoid condition of small bones.

The following day pericardial friction became audible over the whole praecordium and during the succeeding

48 hrs the cardiac dullness extended beyond the apex beat. The blood pressure fell to 90/60 and the generalized lymphadenopathy appeared.

Laboratory Investigations.—Haemoglobin 67 per cent. (Haldane) 9·9 g. per 100 ml.; Colour Index 0·87; White Blood Count 22,000 per c.mm. (80 per cent. polymorphs). Erythrocyte Sedimentation Rate 100 mm./hr (Westergren).

A mid-stream specimen of urine contained a trace of albumin and showed microscopic haematuria, but remained sterile on culture.

Serum proteins 7·25 g. per 100 ml. (albumin 3·5 g., globulin 3·4 g.), electrophoresis showed increased α and γ fractions. The sheep cell agglutination test (Rose, Ragan, Pearce, and Lipman, 1948; modified by Ball, 1950) was positive, and L.E. cells were found in the peripheral blood in significant numbers.

Serial electrocardiograms showed flattened T-waves in all leads. There was no evidence of recent myocardial infarction.

Radiography of the chest (Fig. 2) revealed a globular cardiac shadow with acute cardiophrenic angles, suggestive of a pericardial effusion.

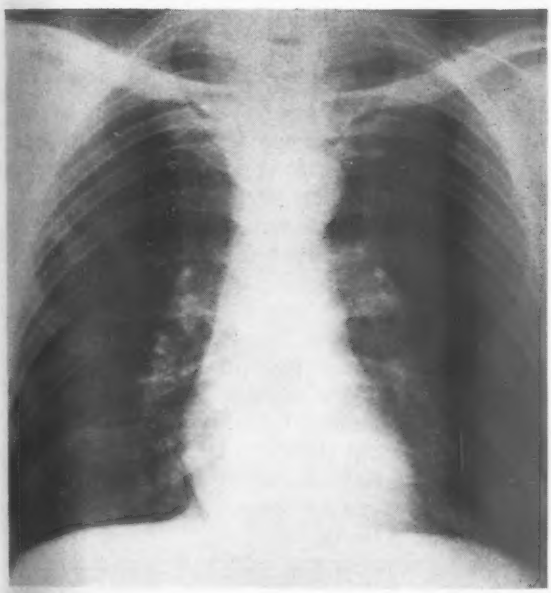


Fig. 2.—Chest radiograph on admission (Case 1).

Progress.—Treatment consisted of rest in bed, full doses of calcium aspirin, oral iron, and local splintage of the most severely affected joints. The patient was discharged from hospital one month later, much improved, but with the pericardial rub still clearly audible; 8 months later he was still well. Examination of the peripheral blood for L.E. cells was then negative, and radiography of the chest showed an improvement (Fig. 3).

Fig. 3.—Chest radiograph after 10 months (Case 1).

Case 2, a housewife, aged 61, was admitted to hospital on 21.10.54; 5 days before she had suddenly developed severe retrosternal pain, made worse by breathing, which had persisted for 3 days.

Previous History.—In 1939, after septicaemia complicated by a lung abscess and a renal carbuncle necessitating nephrectomy, she had started to suffer from chronic rheumatoid arthritis. At the time of her latest admission to hospital she was considerably disabled by arthritis.

Examination.—She was pale, pulse 100 and regular, temperature 98° F., blood pressure 115/60. Severe destructive rheumatoid arthritis involving hands, elbows, knees, and feet.

Pericardial friction was audible down the left border of the sternum, and at the apex of the right lung signs of cavitation could be elicited.

A few small, soft lymph glands could be felt in the neck and axillae and the tip of the spleen was easily palpable.

Laboratory Investigations.—Haemoglobin 44 per cent. (Haldane) 6·5 g. per 100 ml.; Colour Index 0·71; White Blood Count 9,000 per c.mm. with normal differential count. Erythrocyte Sedimentation Rate 40 mm./hr (Westergren).

A catheter specimen of urine was normal on microscopy and remained sterile on culture.

Serum proteins 6·9 g. per 100 ml. (albumin 2·6 g., globulin 4·3 g.), electrophoresis showed an increase in all the globulin fractions. L.E. cells were found in significant numbers in the peripheral blood.

An electrocardiogram showed the typical early changes of pericarditis and elevation of the S.T. segment

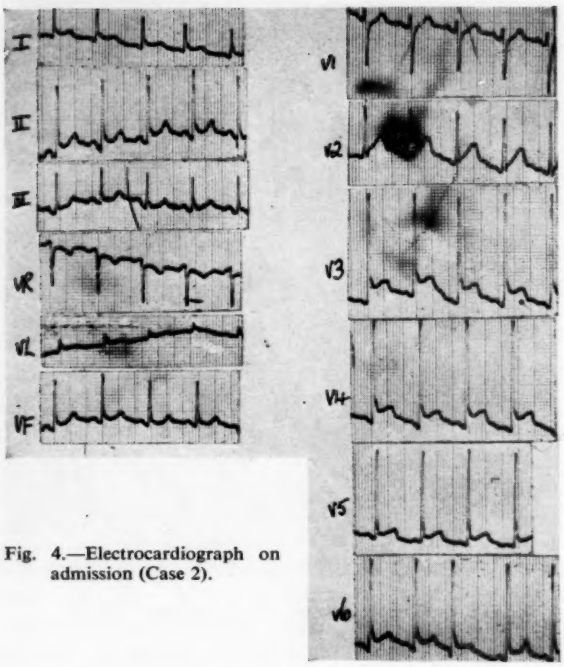


Fig. 4.—Electrocardiograph on admission (Case 2).

with retention of its normal concavity in all leads (Fig. 4).

Radiography of the chest confirmed the presence of a cavity with much fibrosis at the eight apex.

Repeated examination and cultures of the sputum for tubercle bacilli were negative.

Progress.—With rest in bed, full doses of calcium aspirin, and intravenous iron therapy, her condition steadily improved. When she was seen as an outpatient 6 weeks later her haemoglobin had risen to 96 per cent. (Haldane), and the erythrocyte sedimentation rate was 7 mm./hr, but L.E. cells could still be found in the peripheral blood. At her last attendance in June, 1955, she was still well and L.E. cells could no longer be found.

Case 3, a housewife, aged 63, was admitted to hospital on 6.5.54 with severe pain in the left parasternal region, of sudden onset 3 days before, worse on breathing, and accompanied by vomiting.

Previous History.—Radiotherapy had been given for carcinoma of the uterus 13 years previously and shortly afterwards had developed a progressive polyarthritis; 11 years later a colostomy was performed on account of a recto-vesico-vaginal fistula.

Examination.—She was pale, pulse 100 and regular, temperature 100·3° F., blood pressure 120/80. Typical rheumatoid involvement of the hands, wrists, and knees. Apex beat palpable in the fifth left interspace 4 in. from the mid-line, but cardiac dullness extended 1 in. beyond the apex. Pericardial friction was audible over the whole praecordium and remained so for 5 days.

Laboratory Investigations.—Haemoglobin 63 per cent. (Haldane) 9·3 g. per 100 ml.; Colour Index 0·88; White Blood Count 14,000 per c.mm. (78 per cent. polymorphs). Erythrocyte Sedimentation Rate 78 mm./hr (Westergren).

Electrocardiograms showed typical inversion of T.2 with flattened or inverted T-waves in the remaining leads.

Progress.—With rest in bed and intensive aspirin therapy her condition slowly improved. She became apyrexial after one week and her erythrocyte sedimentation rate had fallen to 77 mm./hr when she was discharged 5 weeks later. One year later she was still alive, but was unwilling to attend hospital for examination.

Discussion

Joint involvement is a prominent feature of disseminated lupus erythematosus and most observers agree on an incidence of between 64 and 85 per cent. (Tumulty, 1952; Gold and Gowing, 1953; Jessar, Lamont-Havers, and Ragan, 1953).

Whilst this symptom normally takes the form of arthralgia or a fleeting arthritis with synovial effusions, the occurrence of a chronic deforming arthritis, indistinguishable clinically and radiologically from rheumatoid arthritis, has been reported (Reifenstein, Reifenstein, and Reifenstein, 1939; Friedman, Schwartz, Trubek, and Steinbrocker, 1953; Jessar and others, 1953). In some cases this arthritis has preceded the onset of other features of the disease by considerable periods (Reifenstein and others, 1939; Dubois, 1953a, b). Pericarditis is also a well-established feature of D.L.E. with an incidence in most series of 23 to 43 per cent. (Dubois, 1953a, b; Jessar and others, 1953).

The specificity of L.E. cells in the diagnosis of D.L.E. has recently been the subject of some controversy. A case of acquired haemolytic anaemia in which L.E. cells were found was reported by Lee, Michael, and Vural (1951); it later came to autopsy and was shown to be a case of D.L.E. in which the haemolytic anaemia had been the first manifestation of the disease process.

In the same paper the authors report the finding of a solitary L.E. cell in a patient with primary amyloidosis, but the significance of a single L.E. cell found on one occasion only is open to doubt. The finding of L.E. cells in two cases of penicillin reaction was reported by Walsh and Zimmerman (1953); these patients later developed typical D.L.E. which eventually proved fatal (Dubois, 1953b). L.E. cells have also been reported in myelomatosis and in leukaemia (Fisher and Moyer, 1950).

Opinion now inclines to the view that L.E. cells are a specific finding in D.L.E. We were unable to demonstrate their presence in forty uncomplicated

cases of rheumatoid arthritis attending this hospital from January to June, 1955. Walsh and Egan (1952) found no L.E. cells in cases of rheumatoid arthritis, rheumatic fever, and periarteritis nodosa. No false positives were encountered by Dubois (1953b) in a large series of tests. It seems likely, therefore, that the cases here reported are suffering from a form of subacute D.L.E.

During a 2-year period in a busy general medical unit, only five patients with pericarditis were seen, of whom three are reported above. In two of these, the chest pain was at first thought to arise from cardiac infarction. The possibility that chest pain and pericarditis in a patient with rheumatoid arthritis may be due to the rheumatoid process should not therefore be overlooked.

Summary

(1) Three patients with rheumatoid arthritis and pericarditis are described.

(2) The finding of L.E. cells in two of them is reported.

(3) The significance of these findings is discussed.

We wish to thank Dr. E. W. Skipper for permission to publish these cases, Professor G. M. Wilson for his helpful advice, and the photographic departments of the Sheffield Royal Infirmary and Nottingham General Hospital for the illustrations.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.
Bayles, T. B. (1943). *Amer. J. med. Sci.*, **205**, 42.
Dubois, E. L. (1953a). *Ann. intern. Med.*, **38**, 1265.
—— (1953b). *Arch. intern. Med.*, **92**, 168.
Fisher, G. S., and Moyer, J. B. (1950). *Grace Hosp. Bull.*, **28**, 3.
Friedman, H. H., Schwartz, S., Trubek, M., and Steinbrocker, O. (1953). *Ann. intern. Med.*, **38**, 732.
Gold, S. C., and Gowing, N. F. C. (1953). *Quart. J. Med.*, **22**, 457.
Graef, I., Hickey, D. V., Altmann, V., and Rosenthal, J. (1948). *Proc. N.Y. path. Soc.*, 1948-1949, p. 15.
Jessar, R. A., Lamont-Havers, R. W., and Ragan, C. (1953). *Ann. intern. Med.*, **38**, 717.
Lee, S. L., Michael, S. R., and Vural, I. L. (1951). *Amer. J. Med.*, **10**, 446.
Reifenstein, E. C., Reifenstein, E. C., Jnr., and Reifenstein, G. H. (1939). *Arch. intern. Med.*, **63**, 553.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. Exp. Biol. (N.Y.)*, **68**, 1.
Sokoloff, L. (1953). *Amer. Heart J.*, **45**, 635.
Tumulty, P. A. (1952). *Bull. rheum. Dis.*, **2** (May), p. 17.
Walsh, J. R., and Egan, R. L. (1952). *New Engl. J. Med.*, **246**, 775.
——, and Zimmerman, H. J. (1953). *Blood*, **8**, 65.
Wood, P. (1952). "Diseases of the Heart and Circulation." 2nd ed. Lippincott, Philadelphia.

Péricardite compliquant l'arthrite rhumatismale

RÉSUMÉ

(1) On décrit trois cas d'arthrite rhumatismale et de péricardite.

(2) On signale la découverte de cellules L.E. chez deux d'entre eux.

(3) On discute la portée de cette découverte.

Pericarditis complicando la artritis reumatoide

SUMARIO

(1) Se describen tres casos de artritis reumatoide con pericarditis.

(2) Se señala la descubierta de células L.E. en dos de ellos.

(3) Se discute la importancia de esta descubierta.

BOOK REVIEWS

Rheumatoid Arthritis and Psoriasis Vulgaris. By Tibor Benedek. 1955. Pp. 308, 57 illus. Lithoprinted by Edwards Brothers Inc., Ann Arbor, Michigan.

In this monograph the author presents his investigations and theories into the aetiology, pathogenesis, and inter-relationship of rheumatoid arthritis and a group of erythemato-squamous dermatoses, including psoriasis vulgaris.

He maintains that, by his special "cantharides blister" bacteriological technique, he can demonstrate a state of endoparasitism with the *B. endoparasiticus* (Benedek, 1927) in 90 per cent. of normal healthy individuals, and that this state is perpetuated by transmission from the maternal to the foetal circulation.

The central pathogenetic principle of his theory is a bacterial-allergic inflammatory process occurring in connective tissue, the causative agent being the *B. endoparasiticus*. He states that the intensity of the bacteraemia with this organism in psoriasis is only equalled or surpassed by that found in individuals with rheumatoid arthritis. During this phase of intense bacteraemia the organism escapes from the blood stream into the connective tissue and there provokes an immunobiological reaction. When the cutaneous connective tissue is the main target psoriasis may result, and when the articular tissue is primarily affected rheumatoid arthritis develops. He thus maintains that these cutaneous and articular manifestations are merely different aspects of the same process.

Acceptance of the author's views on aetiology implies acceptance of the existence of a state of permanent endoparasitism. This fundamental claim was first published by Dr. Benedek nearly 30 years ago, but during the ensuing years no adequate corroboratory evidence appears to have been forthcoming in support of his claim. It seems strange, if his claims are correct, that such a fundamental concept should have been so completely ignored and have aroused so little interest in the minds of independent bacteriologists.

The author has answered the question why rheumatoid arthritis and psoriasis are not universal diseases by postulating that a certain type of constitution, or the presence or absence of an unknown factor X, is necessary for the development of the disease state. He holds that the remissions occurring when jaundice is present are due to the temporary sterilization of the blood stream by bile salts, and he discounts the possible effects of increased circulating corticoids in this condition and in pregnancy remissions. He considers that the latter are due to the intravenous desensitization of the maternal tissues by the continuous circulation of heterogenous foetal *B. endoparasiticus*.

In his foreword Dr. Benedek claims to have solved the problem of the aetiology and pathogenesis of rheumatoid arthritis and psoriasis. As a necessary preliminary to accepting his ideas on pathogenesis one must be completely convinced that a state of permanent endoparasitism does in fact exist, for this is the very keystone of his theory, and until incontrovertible bacteriological proof is forthcoming Dr. Benedek's claims must be held in abeyance.

J. H. JACOBS.

Hydrocortisone in Orthopaedic Medicine. By James Cyriax. 1956. Pp. 31. Cassell, London. (5*s*.)

This pamphlet is mainly concerned with the technique of injecting hydrocortisone into various joints and into lesions of the soft tissues. The approaches advised are those commonly used by most centres employing this substance, but credit for the best method for the hip joint should have been given to the two Dutch anatomists, Landsmeer and Koumans (1954),* who described it originally and the 8-cm. needle mentioned is too short to reach the capsule of the hip joint by this approach. It seems doubtful if the number of "thrusts" mentioned by the author are really necessary.

Even in a short account of local hydrocortisone the absence of any reference to the careful work carried out in Rheumatism Centres mostly in the United States on the effect on joint fluid is a serious omission. It has been shown that the substance is taken up by the synovial membrane in a few minutes, not "a few hours" as the author states.

OSWALD SAVAGE.

Rhumatisme chronique. Méthodes thérapeutiques. By F. Coste and M. Bourel. 1956. Pp. 207, 9 figs. Doin, Paris. (1,750 *Fr. frs*; 35*s*.)

This volume describes most of the therapeutic procedures in current use in rheumatic diseases. It contains a simple and practical classification of the arthritides and devotes separate chapters to chrysotherapy, hormones, pyrazolone derivatives, orthopaedic measures, etc. The practitioner is thus able to judge the efficacy of various types of treatment and take his choice. Of necessity there has been curtailment in the description of certain procedures, notably in physiotherapy, and some minor conditions (*e.g.*, carpal tunnel syndrome) have been omitted. On the other hand, there are a number of suggestions that could be pursued with advantage. It seems reasonable, for example, to apply traction to the lower limb in osteo-arthritis of the hip and to do it when the patient is asleep. What is more likely to do good—gentle and continuous traction for 6 to 8 hours every

* Landsmeer, J. M. F., and Koumans, A. K. J. (1954). *Annals of the Rheumatic Diseases*, 13, 246.

night or attendance at a physiotherapy department for 30 minutes, two or three times a week? But how is this extension to be applied by the patient nightly in the privacy of his bedroom? On this point the authors do not enlighten the reader. Minor frustrations also arise from the omission of a list of references, although names are freely quoted in the text. This trend has been noticeable in French medical literature and has two points in its favour: the cost of production is reduced and the majority of readers do not consult the bibliography in any case. Nevertheless, when the specialist reads (p. 120) that the revolting finger deformities seen in rheumatoid arthritis can be corrected under local anaesthesia, his interest is bound to be aroused, but the only clue to technique that he will find is a cryptic "M. Zimmer". In spite of minor blemishes, the therapeutic field is well covered. The methods recommended conform largely with British practice; divergences are to be expected, *e.g.*, the extensive use of deep *x* rays for osteo-arthritic hips, but the area of agreement is far greater. Intra- and peri-articular injection of hydrocortisone and skeletal traction are popular forms of therapy which receive detailed attention, the former being well described in a separate chapter with line diagrams. The French, who have always maintained a more optimistic opinion of the effect of this hormone on Heberden's nodes than practitioners in Great Britain, claim remarkably good results providing not more than 0·1-0·2 ml. is injected into the joint—a larger quantity can give rise to an inflammatory reaction. Of fifteen cases treated by the authors only one received no benefit. Their experience of skeletal traction is extensive and enables them to comment authoritatively on the osteopathic theory that serious intestinal dysfunction can be caused by minute displacement of vertebrae. Coste and Bourel, who have applied skeletal traction (sometimes to an excessive degree) to a large number of patients, have not produced visceral upset in a single case.

Although the book is in paper covers, and colour plates, *x*-ray photographs, and bibliography are omitted, the cost of production is still higher than in Great Britain. The volume is part of a series devoted to medical therapeutics and will have a greater appeal to the general practitioner than to the specialist.

DAVID PREISKEL.

FIRST INTERNATIONAL SYMPOSIUM ON RHEUMATIC FEVER

MEXICO, 1956

On April 30, 1956, and lasting for four full days, there met in Mexico City the First International Symposium on Rheumatic Fever, attended by a large number of physicians from Central and North America and a few from Europe. The meetings were held in the National Institute of Cardiology, a large modern series of buildings lavishly equipped and enthusiastically staffed, directed by Dr. Ignacio Chavez. In its entrance hall there are two large frescos by Diego Rivera, illustrating in a vivid and powerful whole almost every famous figure in the long history of cardiology, from Galen up to Paul D. White and Charles Laubry (including William Heberden holding his *Commentaries*, with his forefinger, no doubt, marking Chapter 70 on "Pectoris dolor"); accurate to the last detail of Stephen Hale's mare or William Withering's foxgloves, these paintings present a wonderful symbol of the unity of medicine.

Dr. Chavez, after welcoming the participants, gave a general outline of the epidemiological problems of rheumatic fever in Mexico. This is estimated to be very common in young people, reaching a figure ten times as high as that given for schoolchildren in the notifying areas of England. Most of the cases referred to the Institute had severe disease of three valves and the Pathological Department usually carried out between one and three *post-mortem* examinations per week throughout the year on patients with acute rheumatic carditis, accumulating thereby a wealth of pathological material with which subsequent speakers from the Institute dealt fully.

A brief but comprehensive review of current concepts of the aetiology of rheumatic fever and rheumatic heart disease was given by Dr. A. Dorfman (University of Chicago), who stressed not only the role of the Group A haemolytic streptococcus but also those possible host-factors which determine why so few of all those exposed to this organism develop rheumatic fever. Dr. E. G. L. Bywaters (University of London) reviewed the immunological aspects of rheumatic fever, including investigations at the Special Unit for Study and Care of Juvenile Rheumatism at Taplow on experimental auto-antibody mechanisms and recent work on the antistreptolysin-O response of children below the age of 5 with rheumatic fever. Contrary to expectations this response was significantly lower than in older children, parallelling what is seen in uncomplicated streptococcal infection. Dr. A. Kuttner (New York University), well known for her work on the prophylaxis of this disease, reviewed the role of the streptococcus, pointing out the many questions which still remain to be answered.

The next sessions dealt primarily with histopathogenesis. Dr. Isaac Costero and his collaborators showed a remarkable series of coloured slides from the vast material of the Institute, illustrating lesions, which in Great Britain would be considered as rarities, such as

tricuspid deformities and a severe type of encephalopathy, only rarely, if ever, seen elsewhere.

The histochemistry of fibrinoid material in the collagen diseases was described by Dr. Paul Klemperer (Mount Sinai Hospital, New York) including results with the ingenious methods such as microspectrophotometry perfected in his laboratory. He was followed by Dr. George Murphy (Cornell University, New York), who gave a detailed account of the lesions produced in rabbits' hearts with repeated streptococcal skin injections, a widespread fibrinoid necrosis involving the myocardial fibres and comparable with the somewhat similar lesions seen in man. Work recently published includes the breeding of a strain of rabbits which show a very high incidence of heart lesions following such inoculations and occasionally a subacute bacterial endocarditis.

Dr. Dorfman outlined the work of his group on the polysaccharide substances in connective tissue with particular reference to experimental diabetes, where a tagging technique showed a decreased turnover of both hyaluronic and chondroitin sulphuric acids and inhibition of polysaccharide synthesis by hydrocortisone.

The clinical picture of rheumatic fever was outlined by Dr. Benedict Massell from his long experience at the House of the Good Samaritan in Boston. He also described controlled studies on the home prevention of streptococcal infection in children who have had rheumatic fever, using for comparison the amount of streptococcal infection amongst the brothers and sisters of these patients in the same environment. Others dealt with specific aspects of the clinical course; carditis was discussed by Dr. Mendoza, rheumatic encepatholopathy by Dr. De Gortari, and rheumatic pneumonitis by Dr. Cuellar (all from the Mexican Institute of Cardiology), and Jaccoud's syndrome by Dr. Bywaters.

Dr. Edward Bland (Massachusetts General Hospital, Boston), discussed the prognosis of patients with aortic regurgitation and the value of the new plastic prosthesis, against a background of the 1,000 cases of rheumatic fever which have now been followed for 20 years by himself and the late Duckett Jones. The electrocardiographic signs of the valvular lesions were described by Dr. Sodi Pallares (Mexico) and a detailed study was presented by Dr. Decourt (Brazil) of the acute phase reactants and electrophoretic protein changes in the serum during the course of the acute disease. Dr. Cesarman (Mexico) talked about chemotherapy and Dr. Robles Gil (Chief of the Department of Rheumatism at the Institute of Cardiology) hormonal treatment. The latter gave an interesting account of the decreased incidence of Aschoff-like lesions in the left auricle at commissurotomy in patients given pre-operative cortisone. After a discussion on mitral commissurotomy, the proceedings terminated with a full discussion of a programme for prophylaxis to be planned on a national scale and to be carried out from the Institute of Cardiology with assistance from the Department of Health.

This ended the formal discussions, but opportunity was given later for informal discussions on many aspects and for seeing something of the Mexican scene.

What impressed the English visitor most was the vigour and enthusiasm of the country, exemplified as much by the Institute of Cardiology as by the enormous amount of new and modern buildings, the virile mural paintings, and the magnificent archeological exhibitions. It was indeed apparent that the coming together in this country of the new world spirit and old world traditions, —the Spanish influence, the cultures of Pre-Colombian civilizations, and the 20th-century civilization,—have created a land of great promise and opportunity.

SOCIETÀ ITALIANA DI REUMATOLOGIA

Fourth Rome Rheumatology Day

At meetings held on February 11 and 12, 1956, papers were given by the following speakers:

PROF. L. J. MICHOTTE (*Brussels*): Surgery in Periarthritis of the Shoulder.

PROF. C. MARINO-ZUCO (*Rome*): Orthopaedic Surgery of the Great Joints.

PROF. P. BARCELÓ (*Barcelona*): The Small Vertebral Joints and Syndromes of Cervical Origin.

PROFS. T. LUCHERINI and E. CECCHI (*Rome*): Pulmonary Disease and Rheumatoid Arthritis.

PROFS. A. MARMONT (*Geneva*) and C. CAMPANA (*Rome*): So-called Visceral Lupus Erythematosus.

PROF. C. CERVINE (*Rome*): Heredity and Constitution in Rheumatology.

Tenth Congress, Milan, 1956

The tenth Congress of the Italian Rheumatological Society was held in Milan on May 30 and 31, 1956, to mark the occasion of the fifth centenary of the founding of the Ospedale Maggiore di Milano. The following papers were given:

Heredity in Rheumatic Disease: U. Teodori and G. G. Neri Serneri.

Biological Effects of the New Steroids on the Action of Cortisone: G. Sala and A. Amira (*Milan*).

Adrenal Function during Treatment with Prednisone and Prednisolone: T. Galli, G. Lamedica, and G. Lotti (*Genoa*).

Effects of Prednisone and Prednisolone on Renal Function: A. Bergamini and B. Bonati (*Modena*).

Prednisone in Rheumatism with special reference to Carditis: G. Casolo (*Milan*).

EMPIRE RHEUMATISM COUNCIL

NINETEENTH ANNUAL REPORT

The nineteenth annual report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual General Meeting held on May 1, 1956, in the State Rooms, St. James's Palace, London. H.R.H. the Duke of Gloucester, President of the Council, was in the Chair.

The Chairman first recorded the loss of the Council's distinguished Founder, Lord Horder, who died on August 13, 1955, at the age of 84; and also that of Dr. C. W. Buckley, a valued member of the Scientific Co-ordinating Committee, who died on May 28, 1955, in his 81st year.

The debt which the Empire Rheumatism Council owed to the late Lord Horder, whose reputation, like his influence and interests, was world-wide, was difficult to describe. He was the first chairman of the Council on its foundation in 1936, and only resigned the chairmanship in 1953, when he was appointed Emeritus Chairman. The Council's prosperity was due in large measure to Lord Horder. From all corners of the globe there had been received tributes to his pioneer work and to his magnetic influence. Right to the end he kept his closer interests and friendships in repair, and he left a kindly memory for which many must be grateful.

Dr. Buckley, one of the pioneers of rheumatism research and treatment, was also a valued friend. As a member of the Scientific Advisory Committee and editor of the *Annals* from the inception of the Council, and later as chairman of the Education Sub-Committee, his services were highly valued. He spoke with authority and was listened to with respect.

Chair of Rheumatology

During the year under review the work of the Manchester Rheumatism Centre had been consolidated and expanded, a new biophysics section having been added to the otherwise well-equipped laboratories. Both clinical and laboratory research was being energetically pursued, and there was no doubt that the creation of the University Chair of Rheumatology had been a great stimulus to work in the field of rheumatism.

A memorandum compiled by Professor Kellgren, the first professor of rheumatology, illustrated the general activities and wide scope of a university department of rheumatology. During 1955 Professor Kellgren had participated by invitation in the dedication ceremonies at the opening of the Hospital for Special Surgery in New York, as the official delegate of the council, and had also taken part in their scientific programme.

Research

E.R.C. Fellowships.—One of the E.R.C. Fellows, Dr. J. K. Norymberski (Director of Medical Research within the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases) reported as follows:

> Last year's work included the following investigations (carried out with the collaboration of Miss J. I. Appleby, Mrs. S. Ingall, Dr. Jean McKenna, Mr. R. D. Stubbs, and Dr. G. F. Woods):
>
> (1) *Partial reductions of steroid hormones and related substances.*—The metabolic transformations of steroid hormones involve a series of reductive steps, each occurring at one site of the molecule only. Such partial reductions have now been carried out by conventional chemical means and a number of compounds of biologic interest was prepared. The reducing action of zinc in boiling aqueous acetic acid received particular attention; the reagent was found to convert steroidal dihydroxyacetones into 20 : 21 ketols unsubstituted at $C_{(17)}$ (*e.g.* cortisol into corticosterone).
>
> (2) *Determination of "zinc-resistant 17-ketogenic steroids".*—In contradistinction to dihydroxyacetones the other two sub-groups of 17-ketogenic group of steroids, *i.e.* 17 : 20-diols and 17 : 20 : 31-triols, resist the action of zinc and consequently retain their 17-ketogenic property. This observation led to the development of an analytical method for the determination of "zinc-resistant 17-ketogenic steroids". The assay can reveal a certain type of abnormal excretion pattern which, so far, was found in pregnancy and in the adrenogenital syndrome.
>
> (3) *Excretion of corticosteroids in pregnancy.*—The excretion of total 17-hydroxycorticosteroids in pregnancy increases gradually to reach maximal values (10-30 mg./day) at delivery and falls during the following week to normal levels (16-14 mg./day). The corresponding increase of urinary 21-deoxyketols (a sub-group of 17-hydroxycorticosteroids; see last year's report) is more pronounced (1-3 mg./day at delivery; 0·1-0·3 mg./day in non-pregnant women).

A paper was presented at the International Congress of Biochemistry in Brussels by Dr. Norymberski on work done in collaboration with Mr. R. D. Stubbs:

> *Differentiation of Urinary 17-ketogenic Steroids.*—Treatment with zinc dust in 50 per cent. aqueous acetic acid transforms 17 : 21-dihydroxy-20-oxosteroids into products which no longer can be converted into 17-oxosteroids by sodium bismuthate. Under identical conditions other 17-hydroxycorticosteroids retain their 17-ketogenic property and 17-ketones are unaffected. This selective elimination of 17 : 21-dihydroxy-20-oxosteroids as potential precursors of 17-oxosteroids can be brought about in the urine and hence a simple means becomes available for the differential analysis of urinary 17-ketogenic steroids.

The Council's laboratory at the Hospital of St. John and St. Elizabeth had continued to be used as an adjunct by Miss I. H. M. Muir, another E.R.C. Fellow working at St. Mary's Hospital, Paddington. Professor G. W. Pickering, Director of the Medical Unit at St. Mary's

Hospital, Paddington, reported on Miss Muir's work as follows:

> During the course of the year the work has been largely concentrated on the structure of connective tissue polysaccharides and has been devoted to (*a*) the development of new and improved techniques for isolating and studying these substances, and (*b*) the study of the structure of highly polymerized chondroitin sulphate which is one of the chief polysaccharides of connective tissue and which has hitherto been mainly studied in a comparatively degraded form.

(*a*) *Developments of Technique*

(1) Paper chromatography of large molecules presents very considerable difficulty, but if successful will afford qualitative and semi-quantitative information with extremely small amounts of material. It should therefore be suitable for the study of biopsy specimens. After an extensive search a suitable paper and solvent system was found which clearly separated degraded chondroitin sulphate from the highly polymerized material, so that not only could the two materials be distinguished from each other, but the approximate amounts in any given sample or mixture could be estimated. This can only otherwise be done by complicated indirect physical measurements obtained, for example, from sedimentation studies on the ultracentrifuge.

(2) One of the main difficulties to be met in the study of the chemical structure of connective tissue is that of isolating and purifying polysaccharides from protein, without degrading the polysaccharides. Various basic organic substances have been studied, some of which may prove generally useful, as they do not precipitate such proteins as acid-soluble collagen, gelatin or plasma proteins, but form very insoluble salts with acidic polysaccharides such as heparin and chondroitin sulphate. The free polysaccharide can be regenerated without any change of physical or chemical properties. This work is being further investigated.

(3) The accurate micro-estimation of sulphate is required to determine the structure of pure sulphated polysaccharides, and also affords a measure of the amount of such polysaccharides in whole connective tissue. The methods which are available are not only tedious but often erratic. An improved modification of the benzidine sulphate method has been developed which has proved to be quite reliable and accurate at 100 μg. SO_4, although very much smaller quantities can be determined with some loss of accuracy.

(*b*) *Structure of Highly Polymerized Chondroitin Sulphate*

Chondroitin sulphate is generally extracted from cartilage under alkaline conditions. The product obtained is of comparatively low molecular weight and is a simple polymer of glucuronic acid and N-acetylgalactosamine sulphate. However, when chondroitin sulphate is extracted with neutral calcium chloride a very viscous product is obtained, with a molecular weight 10-15 times greater than material obtained by alkaline extractions. The structure of this highly polymerized chondroitin sulphate has been investigated after extensive purification, both by analytical methods and by the use of enzymes.

Analyses showed that this material was not a simple polymer of glucuronic acid and N-acetylgalactosamine sulphate, but contained a small proportion of amino-acids, which have been identified by paper chromatography. Further purification did not change the amino-acid pattern. The substance was stable to heat and did not flocculate with any protein precipitants, but it was very rapidly degraded by weak alkali.

Pure proteolytic enzymes had different effects on the viscosity and chromatographic behaviour. Some loss of viscosity was produced by trypsin chymotrypsin and carboxypeptidase, but the behaviour on paper chromatograms did not change. Pepsin caused a 48 per cent. fall in viscosity and some change in chromatographic behaviour. However, crystalline papain brought about an immediate and large fall in viscosity, 83 per cent. of the viscosity being lost in 15 minutes. The product behaved in a similar manner on paper chromatograms as the alkali degraded polysaccharide, and the viscosities of the two degraded products showed that they had similar molecular weights. Papain digestion also produced some dialysable sulphate and hexosamine, showing that small fragments had been broken from the polysaccharide molecule. Inhibition studies and control experiments proved that the effect was genuinely due to papain and not to an impurity. The papain-digested polysaccharide did not contain amino-acids.

It is concluded from these results that chondroitin sulphate exists in tissues as a complex of large molecular weight consisting chiefly of polysaccharide cemented by small amounts of peptide or protein, which is destroyed by papain and alkali. Since a large fall in molecular weight of a highly asymmetric molecule such as chondroitin sulphate produces a marked change in physical properties, it is possible that if such a breakdown occurred in the tissues there would be a marked change in mechanical properties, the tissues becoming less elastic and less resilient. Some of the pathological and degenerative changes of connective tissue might thus be explained.

Work is being concentrated on this aspect because if this complex is an important structural feature, complete proof must be obtained and any differences between different tissues and between normal and pathological tissue established.

Effect of Pathologial Fluids and Sera on the Chondroitin Sulphate Complex.—Sera and synovial fluids from the knee joint of four cases of acute rheumatoid arthritis were tested for their effect on the chondroitin sulphate complex, in case they contained an enzyme having a similar effect to that of papain on the polysaccharide, but no fall in viscosity or change in chromatographic behaviour was observed. However, as the polysaccharide was not of human origin, the negative result is not conclusive.

A paper published by Dr. W. C. Boake and Miss Muir in *The Lancet* is abstracted on p. 206 of this issue.

The following is an abstract of a paper given by Miss Muir to the Medical Research Society:

> *A Highly Polymerized Chondroitin Sulphate Complex from Cartilage.*—Chemical investigation of the structure of chondroitin sulphate from cartilage has been mostly carried out on material extracted under alkaline conditions which yield relatively degraded material, as judged by molecular weight. However, Blix and Snellman (1945) have obtained the polysaccharide with ten to fifteen times the molecular weight, namely 150,000-250,000, by extraction with neutral 10 per cent. $CaCl_2$. This material was very sensitive to alkali, being rapidly degraded by 0·01N. NaOH.
>
> Chondroitin sulphate was prepared by this method from hog laryngeal cartilage and purified by precipitating with $Co(NH_3)_6Cl_3$ (Mathews and Dorfman, 1953; Mathews, 1955). The polysaccharide thus obtained was noticeably viscous; the relative viscosity of 0·5 per cent. solution in water was 6·1 at 25° C. It contained 26·3 per cent. hexosamine, 14·1 per cent. sulphate and 4·47 per cent. nitrogen. By difference, the non-hexosamine nitrogen was 2·4 per cent. This was due to the presence of amino-acids, as shown by paper chromatography. Further attempts to purify the polysaccharide did not reduce the non-hexosamine nitrogen or change the amino-acid pattern, which was remarkable in showing almost no aromatic amino-acids. This was confirmed by ultra-violet spectroscopy.
>
> The material was not stable above *p*H 8·5. In 0·015N. NaOH the viscosity diminished rapidly, reaching a limiting value. The polysaccharide was stable to heating at 100° C. for 30 minutes in water. No flocculation occurred either on heating or on treatment with protein precipitants.
>
> The viscosity was affected to different degrees by crystalline proteolytic enzymes. Carboxypeptidase, trypsin, and chymotrypsin caused 2 to 8 per cent. reduction in viscosity in 15 minutes, finally reducing the viscosity by 25-28 per cent.

Pepsin reduced the viscosity by 38 per cent. in 15 minutes, and finally by 48 per cent. Unlike these enzymes, papain, activated by cysteine and versene, caused an immediate and large fall in viscosity. The viscosity was reduced by 80 per cent. in 10 minutes and finally by 83·5 per cent. This effect was completely inhibited by 10^{-4}M p-chloromercuribenzoate and therefore was not due to contamination of papain by papaya lysozyme (Smith, Kimmel, Brown, and Thompson, 1955). Treatment with papain liberated 4 to 6 per cent. of dialysable hexosamine and sulphate, showing that some comparatively small fragments had been split from the molecule.

Paper chromatography of chondroitin sulphate proved a sensitive method for distinguishing between degraded and undegraded chondroitin sulphate. 45 per cent. (v/v) n-propanol/55 per cent. 0·2M boric acid was used with Whatman No. 2 papers. Papain-digested polysaccharide moved as a compact spot with R_F=0·58. Alkali-degraded material behaved similarly. Untreated material remained at the origin, as did material treated with those proteolytic enzymes, which only caused small changes of viscosity. Partially degraded polysaccharide showed both the spots and intermediate streaks.

It is suggested that chondroitin sulphate normally exists as a complex of large molecular weight composed chiefly of polysaccharide cemented by a small amount of polypeptide or protein, which is destroyed by papain and by alkali. Since changes of molecular size of a highly asymmetric molecule such as this will produce large changes in physical properties, some of the degenerative changes of connective tissue such as loss of elasticity or increased permeability could perhaps be explained by a breakdown of the polysaccharide complex by a proteolytic enzyme.

Blix, G., and Snellman, O. (1945). *Ark. Kemi Min. Geol.*, **19A**, No. 32.
Mathews, M. B. (1955). *Fed. Proc.*, **14**, 252.
——, and Dorfman, A. (1953). *Arch. Biochem. Biophys.*, **42**, 41.
Smith, E. L., Kimmel, J. R., Brown, D. M., and Thompson, E. O. P. (1955). *J. biol. Chem.*, **215**, 67.

Dr. Madeline Keech had been appointed a third E.R.C. Fellow as from October 1, 1955; she was working principally in Professor Tunbridge's department at the General Infirmary, Leeds, with some additional clinical work in the Rheumatic Clinic with Professor Hartfall. Her special project was to observe the morphological changes that occur in collagen, elastin, and connective tissue under the action of enzymes, and the effects of denaturation of collagen and elastin, prepared in different ways and subjected to the action not only of enzymes but also of physical agents. Having obtained certain basic information, Dr. Keech intended to proceed to the analysis of changes in connective tissue resulting from degenerative changes and disease processes, and to examine some of the basic pathological changes associated with arterial degeneration, osteo-arthritis, and particularly the rheumatic infections. It was hoped that such research might yield results of fundamental importance.

Geigy Travelling Fellowships.—Out of the Geigy Travelling Fund the Council had been able to depute Dr. H. F. West as an official delegate to the Annual Meeting of the American Rheumatism Association held in San Francisco in June, 1955.

Dr. Malcolm Thompson, the first travelling fellow, of the Rheumatic Unit, Northern General Hospital, Edinburgh, had recently returned from the U.S.A. where he had received an honorary appointment as Clinical and Research Fellow to Harvard University, and had worked in the arthritis unit of the Massachusetts General Hospital, under the direction of Professor Walter Bauer.

Dr. Thompson's report at the end of his 9 months' tour was an informative document:

> Work was done on the methodology of the estimations of ascorbic and dehydro-ascorbic acids, and of coeruloplasmin. The plasma levels of these substances were estimated in normal subjects as well as in patients suffering from rheumatoid arthritis and patients with various other diseases. Although abnormalities in ascorbic acid metabolism were demonstrated in rheumatoid arthritis, similar abnormalities were found in many other diseases involving inflammation, tissue damage and new growth. Raised levels of plasma coeruloplasmin were demonstrated in patients suffering from rheumatoid arthritis, but again, raised values were recorded in a variety of illnesses, especially those in which inflammation, tissue damage, and new growth were involved.
>
> Studies on capillary resistance revealed abnormally low values in a high proportion of rheumatoid patients, compared with control subjects. Further studies are being made to determine the significance of this finding, which accords with recent histological work indicating widespread lesions of small blood vessels in the early stages of rheumatoid arthritis.

Dr. Thompson had also visited the principal rheumatic and rehabilitation centres in the Eastern and Mid-Western States of the U.S.A. and in Canada; he had attended the 1955 meetings of the American Rheumatism Association and the Canadian Rheumatism Association, and had presented a paper at the latter meeting.

The second Geigy Travelling Fellow, Dr. J. Sharp (Lecturer in Rheumatic Diseases, Manchester University), had just left for a study tour relating to ankylosing spondylitis in the U.S.A.

The third Geigy Travelling Fellow, Dr. J. Ball (Senior Lecturer in Pathology in the Rheumatism Centre, Manchester University), had visited leading research centres and attended meetings in San Francisco and Atlantic City. His report included the following observations:

> At the Armed Forces Institute of Pathology (Washington) methods for cutting histological sections of compact bone had been devised. The possibilities of tissue culture for studies of connective tissue metabolism had been re-explored with considerable success at the Presbyterian Hospital (New York) and researches using this method were in progress at other rheumatism centres. At the Rockefeller Institute tissue culture had proved useful in demonstrating the effects of anticollagen antibodies. At Madison, studies on experimental Lathyrism indicated another useful approach to connective tissue problems. Combined histological and immunological studies at Johns Hopkins Hospital had clarified the pathogenesis of experimental serum disease. Chemical methods were being widely used in studies of the sheep cell agglutinating factor; and an essentially chemical method of quantitating this factor was described

at the June meeting of the American Rheumatism Association. Dr. Ball also noted recent work at the Histochemical Laboratory (Columbia University) indicating that the primary nuclear abnormality in D.L.E. involved nuclear histone rather than desoxyribose nucleic acid.

A travelling fellowship had also been awarded to Dr. E. J. Holborrow, of Taplow, Berkshire, who would be leaving for America in the autumn.

Apart from the educational value of the Geigy Fellowships, they assisted in preparing fellows for appointment to consultant status, and Dr. Malcolm Thompson had recently been appointed consultant to the Royal Victoria Infirmary, Newcastle-on-Tyne.

Other Projects.—The following report had been submitted by Drs Robertson and Chapman, who were carrying out steroid research at the West London Hospital:

> During the past 6 months we have been following the 17-hydroxycorticosteroid output in urine from some fifty in-patients and out-patients from this hospital and the Hospital of St. John and St. Elizabeth. This has been done in collaboration with the Department of Rheumatism, in order to assess the degree of adrenal stimulation attained with the administration of ACTH, the results being correlated with the clinical findings.
>
> In all patients the urinary output of 17-hydroxycorticosteroids is estimated for some days before treatment is started, so that a base line or control period can be established. After this daily and then weekly or bi-weekly estimations are performed. The method of Norymberski (*Biochem. J.*, 1955, **60**, 453) is being used for the steroid measurement.
>
> Some preliminary difficulties have now been overcome and patients are being assessed clinically every two or three weeks and biochemically at least weekly and in some cases much more frequently. It has been found that with a moderate level of adrenal stimulation with a daily injection of ACTH, as measured by the output of urinary 17-OHCS, there is suppression of the symptoms of rheumatoid arthritis. So far it has been difficult to achieve a constant level of adrenal stimulation.

The Council had continued to support the work of Dr. E. Wittkower, Assistant Professor of Psychiatry, McGill University, Montreal, Canada, in his "Study of Rheumatoid Arthritis in Two Contrasting Communities".

The results of the first year's Multi-Centre Controlled Trials comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis had been published in the *Annals of the Rheumatic Diseases* (1955, **14**, 353).

A supply of delta-hydrocortisone had been offered to the Council by Messrs. Boots Pure Drug Co. Ltd. and Upjohn of England, and various clinical centres had been approached regarding the use of this drug.

Dr. M. Bassiouni, Ph.D., who had received a grant to cover 6 months' work at the Canadian Red Cross Memorial Hospital, Taplow, to enable him to continue his research into the estimation of heparin-like substances in blood tissues, had reported as follows:

> It was observed during the isolation of heparin from rheumatic patients' blood that a fine metachromatic precipitate was included in the crude dye precipitate which was not present in similar extracts from normal blood. Such metachromatic precipitate suggested that it may include an acid polysaccharide. Studies on paper electrophoresis using a modified procedure confirmed this suggestion since it had an intermediate electrophoretic mobility between beef heparin and human chondroitin sulphate under specified conditions of potential gradient of time. It had a distinct anti-coagulant activity with an A/C ratio of 37. Its complex with the basic dye Azure A has a maximum absorption spectrum at 580 mμ compared with absorption maximum of 620 mμ and 520 mμ for human chondroitin sulphate and beef heparin. Using large amounts of blood collected from cases of acute rheumatic fever it has been shown that this acid polysaccharide was mainly derived from the white blood cells; that present in plasma is probably liberated from these cells. However, this acid polysaccharide was found to be present in variable degrees in 4 ml. blood samples from various other diseases.

Dr. S. C. Milazzo, M.B., M.R.A.C.P., of the Canadian Red Cross Memorial Hospital (Special Unit for Juvenile Rheumatism), Taplow, who had also received a grant for research, reported as follows:

> There is evidence which suggests that certain rheumatic diseases such as rheumatic fever and disseminated lupus erythematosus, and possibly others, may be caused by the patient producing antibodies against components of his own tissues. Except in the case of the red blood cells these antigenic tissue components have not been extracted and adequately studied, so that an essential tool for the study of this hypothesis has been lacking.
>
> The aim of the work at present in progress has been to extract an antigenic substance which is present in reticulin fibres and basement membranes in many parts of the body, as shown by Cruickshank and Hill in Edinburgh. A simple method has been devised by which this antigen and antibody to it can be demonstrated *in vitro*. It has been possible to prepare a fairly pure but insoluble preparation of the antigen by removing the cellular material from renal cortex by trypsin digestion and thorough washing with saline. Attempts using various methods to extract soluble antigen from this preparation are in progress, and if successful will make available a useful tool for further research into the auto-antibody hypothesis.

Equipment and Apparatus.—A grant had been made to Dr. G. D. Kersley for the purchase of a "Uvispek" spectrophotometer for the South West Regional Rheumatism Research Unit, and to Dr. Ernest Fletcher for "a continuous electrophoretic machine" for his unit at the Royal Free Hospital, London.

Under the direction of Prof. Sir Stanley Davidson, equipment and apparatus had been purchased for the new Research Laboratories at the Northern General Hospital, Edinburgh.

Certificates of good order had been received during the year in all instances from the centres where equipment had been purchased by the Council.

Mobile Field Unit.—This would be established in the first instance for a period of 3 to 5 years, and would probably be based in the early stages at Manchester University. It was envisaged that such a unit would in due course undertake projects anywhere, including possibly the Dominions. Prof. J. H. Kellgren had agreed to give the benefit of his experience and advice on survey work to Dr. J. S. Lawrence, who had recently been appointed Medical Director of the unit, and would shortly be visiting other centres in Great Britain, Europe, and the United States, where field studies of rheumatic diseases were in progress, to obtain further information about the methods of survey and the most suitable staff and equipment.

It had been felt advantageous to accept an offer made by the Deputy Medical Officer of Health for Cornwall, Dr. E. R. Hargreaves, to undertake additional preliminary survey work of a similar nature in that county, so that his findings could be correlated with the whole scheme of field research; Dr. Fearnley's proposals for a survey on parallel lines to be undertaken in Gloucestershire would also be included in the general scheme. A clinical, statistical, and radiological team would be appointed in due course, and it was estimated that a capital expenditure up to a maximum of £30,000 for equipment and £7,000 per annum for running expenses would be incurred.

Prof. Kellgren had written as follows:

> In rheumatism as in other diseases, prevention is ultimately likely to be more effective than cure, and it is for this reason that the council has decided to endow a field unit for the study of aetiology and prevention of the rheumatic diseases. Dr. J. S. Lawrence, who has already done important field work on the problem of rheumatism among coal miners, has been appointed clinical director of the new field unit. The field unit will further develop methods of assessing rheumatic diseases in the general population; from this important information about causation and prevention may emerge. But in view of past experience in the mining industry it seems likely that occupational factors may be very important and it is anticipated that other industries and possibly agriculture may wish to avail themselves of the services which such a field unit can provide.

A scheme conforming with the general survey was also proposed in the Wensleydale area of Yorkshire by Leeds University; it was agreed that this work should be co-ordinated with that of Dr. J. S. Lawrence, especially in the matter of radiology as experience had already shown that many technical difficulties arose in carrying out a radiological survey.

EDUCATION

Handbooks.—The *Rheumatoid Arthritis Handbook*, published by the Council for doctors to issue to their patients had proved an unqualified success. Local health authorities throughout the country had requested the handbook in large quantities and large indents were still being received. Nearly 20,000 copies had been distributed free of charge in this way, and the Council had also gladly acceded to requests from the Queen Elizabeth Hospital, Rotorua, New Zealand, and from the Arthritis and Rheumatism Foundation, New York, for permission to reprint the handbook locally.

An *Osteo-Arthritis Handbook* was in course of preparation, and the Council was greatly indebted to Dr. Dudley Hart and Mr. Lloyd Roberts for producing a really excellent publication, and to Mr. Leslie Starke for so generously illustrating both handbooks free of charge. Copies of both would continue to be supplied free upon application to the General Secretary.

Consultants' Conference.—The first Consultants' Conference was held with the distinguished co-operation of Sir Francis Fraser (Director of the British Post-Graduate Medical Federation) from March 24 to 26, 1955; the first two days at the Arthur Stanley Institute, Middlesex Hospital, and the final day at the Post-Graduate Medical School of London, Hammersmith. The conference had been opened by Sir Francis Fraser, and distinguished rheumatologists and specialists lectured and demonstrated on a wide range of subjects. In view of the widespread interest aroused, it had been decided to hold a second Consultants' Conference early in 1956.

The Council was deeply indebted to Dr. Oswald Savage, the Hon. Medical Secretary, for the undoubted success of the conference.

Royal Society of Health Exhibition.—The Council had participated in the exhibition at Blackpool from April 24-27, 1956. Drs Fletcher and Mason, with the assistance of Prof. Kellgren, undertook to be responsible for the stand.

Heberden Society.—The Council had unanimously decided to continue to assist the Heberden Society by an annual grant of £100. This Society was doing extremely valuable work in arranging lectures and demonstrations at centres throughout the country on clinical aspects of the rheumatic diseases. This year's President was Prof. R. E. Tunbridge.

Medical Libraries.—The Council agreed to renew its annual grant to the libraries of the British Medical Association and the Royal Society of Medicine respectively for the provision of books on arthritis and rheumatism.

"Annals of the Rheumatic Diseases."—Accounts of the activities of the Council, of the Heberden Society, and of the British Branch of the European League against Rheumatism, had appeared in the *Annals*, published quarterly by the B.M.A. This was the authoritative

medium for the publication of developments in research and teaching in all fields of rheumatism, and general practitioners and others throughout the country were recommended to subscribe to the *Annals* so that they might be kept conversant with modern trends. As and when more material became available, it was hoped to increase the publication of the *Annals of the Rheumatic Diseases* from four copies to six copies per annum.

World Health Organization.—The Executive Committee had accepted an invitation to become a "sponsoring body" of the United Kingdom Committee for W.H.O., and had nominated for appointment Dr. Ernest Fletcher and Dr. G. R. Fearnley as the Council's representatives on their Executive Board.

Commonwealth

By invitation of the Minister of Health, New Zealand, the Australian Rheumatism Council, and the Council of the Royal Australasian College of Physicians, and with the endorsement of his colleagues, the Chairman had visited these two dominions towards the end of 1955 as the official representative of the E.R.C. He carried with him a personal message from their Royal President to the Governors-General of Australia and New Zealand, and from the Rt. Hon. Iain Macleod (Minister of Health) to the Minister of Health, New Zealand. He was grateful to His Royal Highness for having graciously received him personally both before and after his visit and for his kindly interest in the tour.

He had visited all the chief medical centres and many lesser ones in both countries, and at all the main centres he carried out a prearranged programme of lectures, giving clinical demonstrations and holding conferences. He had also given several broadcast talks, some of a more popular nature. Everywhere he had been received most hospitably, both officially and privately. A detailed account of his itinerary and of his activities in both dominions was contained in the official report (which had been accepted by the Commonwealth Sub-Committee of the Council and by the Executive Committee), and appeared as a supplement to the Annual Report.

Dr. G. N. Watson, on his recall to Australia, left vacant the London representation of the Australian Rheumatism Council on the Commonwealth Sub-Committee, and Dr. S. C. Milazzo, M.R.A.C.P., had been appointed at their suggestion in his stead.

Contact has been established with Dr. Mark Horwitz, of Cape Town, with a view to establishing an affiliated autonomous South African Rheumatism Council in that country. It is hoped that by next year this will be a *fait accompli*.

Administration

It had been recommended that the key administrative committees, *viz.* Executive Committee, Finance Committee, and Scientific Co-ordinating Committee, be re-elected for 1956-57. The Chairman said that he could not refrain from paying special tribute to Dr. Oswald Savage for so ably deputizing as acting Chairman of the Council during his absence in the Antipodes, and for the great help he had rendered to Mr. R. V. Howell, the able general secretary, during that time in the many problems which had come to hand, and also to Prof. Tunbridge for his guidance and wisdom as chairman of the Scientific Co-ordinating Committee.

Conclusion

In the past year the Council had extended its activities in all directions and had been greatly encouraged by the generosity of subscribers and donors which had supported its efforts to overcome the rheumatic disorders which caused more absenteeism and invalidity than any other known malady.

SOCIEDAD ESPAÑOLA DE REUMATISMO

Officers for 1956

President: Dr. P. Barceló (*Barcelona*)
Vice-President: Dr. J. San Roman Rouyer (*Madrid*)
Secretary: Dr. L. Sans Solá (*Barcelona*)
Deputy Secretary:
Dr. Jesus Grinda (*Madrid*)
Treasurer: Dr. E. Batalla Boixet (*Barcelona*)
Committee Members:
Dr. R. Cirera Voltá (*Barcelona*)
delegado en la Liga Europea
Dr. F. Diez Blanco (*Valladolid*)
Prof. J. Gibert Queraltó (*Barcelona*)
Dr. A. Hernández Ros (*Madrid*)
Dr. A. Jiménez Roldan (*Malaga*)
Dr. C. Morcillo Hervas (*Jaen*)
Dr. V. Roig Olmos (*Valencia*)
Dr. J. L. Usobiaga (*Bilbao*)
Dr. J. Mª Vilaseca Sabater (*Barcelona*)

HEBERDEN SOCIETY

ANNUAL REPORT, 1955

It is with the deepest regret that the passing is recorded of two of our most revered colleagues and past presidents, the Rt. Hon. the Lord Horder and Dr. C. W. Buckley. Both of them were honorary life members of the Society, elected for their distinguished services in the field of rheumatism; their passing is a profound loss to the Society and their wise counsel and valuable guidance will be greatly missed.

In 1954 the annual general meeting approved the institution of a new category of membership—"Overseas Members". This category was designed for those who had been active members of the Society, but had taken up permanent appointments in the dominions or overseas, such members to enjoy the same privileges as formerly held and their subscriptions to be continuing.

During 1955 a review was made of the present distribution of members between rheumatology, physical medicine, general medicine, etc., and it was agreed that this situation should be examined annually, bearing in mind that the major interest of the Society is rheumatology. Accordingly, the Annual General Meeting has approved a revision of Rule 6.

The following new members have been elected:

In 1954 Ordinary Members: Dr. B. Clive Nicholson and Dr. N. R. W. Simpson;

Associate Members: Dr. W. R. M. Alexander, Dr. L. J. Barford, Dr. H. Rhys Davies, Dr. R. I. Meanock, and Dr. A. T. Richardson.

In 1955 Ordinary Members: Dr. Alan St. J. Dixon, Dr. J. H. Jacobs, and Dr. J. Sharp.

Associate Members: Dr. J. Ball, Mr. J. C. F. Cregan, Dr. Maurice Jeffrey, Dr. Madeline Keech, Mr. G. C. Lloyd-Roberts, and Dr. Malcolm Thompson.

Dr. F. Wrigley, on returning to reside in the United Kingdom, has reverted from overseas to ordinary membership.

The following resigned their ordinary membership:

Dr. J. H. H. Dunn
Dr. R. R. H. Lovell
Dr. Brandon Lush.

The total ordinary membership on January 1, 1956, was 97, and the associate membership 18.

Activities

The first clinical meeting of 1955 was held by permission of Dr. Ernest Fletcher at the Royal Free Hospital on February 18. Papers were presented by the following speakers: Dr. J. H. Jacobs (*London*), Dr. Clifford Rose (*London*), Mr. Charles Gray (*London*), Mr. R. Markham (*London*), and Dr. A. St. John Dixon (*Bucks*); demonstrations were given by Dr. A. T. Richardson (*London*) and Dr. E. Hess (*London*) (*Annals*, **14**, 105).

Clinical meetings were held by permission of Dr. H. F. West at the Nether Edge Hospital, Sheffield, and at the Edgar Allen Physical Treatment Centre, Gell Street, Sheffield, on July 1 and 2. Papers were presented by the following speakers: Dr. G. R. Newns (*Sheffield*), Drs Eunice Lockey and A. J. Anderson (*London*), Dr. T. L. Pilkington (*Sheffield*), Dr. H. F. West (*Sheffield*), Prof. D. H. Collins (*Sheffield*) Dr. R. Sougin-Mibashan, (*London*), and Dr. J. S. Lawrence (*Walkden Miners' Clinic, Manchester*).

A visit to Chatsworth House, arranged by Dr. West, was followed by dinner at The Peacock, Baslow (*Annals*, **14**, 301, 302).

The Heberden Round was conducted by Dr. F. Dudley Hart at the Westminster Medical School, in the Meyerstein Theatre, on May 6, 1955. A preliminary Report of the Empire Rheumatism Council Long-Term Cortisone/Aspirin Trial was presented by Dr. E. G. L. Bywaters (*Berks*), Dr. Ifor Williams (*London*), Dr. E. Lewis-Faning (*Cardiff*), and Dr. F. Dudley Hart (*London*) (*Annals*, **14**, 212).

The Heberden Oration for 1955, which was to have been given by Dr. Walter Bauer at the Royal Society of Medicine on October 21, had unfortunately to be cancelled because of the postponement of Dr. Bauer's visit to Europe.

The Annual Dinner was held on November 25 at the Royal College of Surgeons. Among the guests present were Viscount and Lady Nuffield, Sir Hubert and Lady Houldsworth, Mr. and Mrs. Farrer-Brown, Mr. and Mrs. Sanderson, Dr. Hugh Clegg, and Dr. I. Douglas-Wilson.

The Annual General Meeting was held on November 25 and 26, 1955, at the Royal College of Surgeons. Papers were presented by the following speakers: Dr. J. Sharp (*Manchester*), Dr. H. F. West (*Sheffield*), Prof. J. H. Kellgren (*Manchester*), Dr. J. S. Lawrence (*Manchester*), Dr. V. Wright (*Stoke Mandeville*), Dr. D. S. Jackson (*Manchester*), and Drs Ian Gilliland, I. Isdale, and E. M. Abdel-Wahab, introduced by Dr. E. G. L. Bywaters (*Postgraduate Medical School, London*) (*Annals*, **15**, 81).

Grant-in-Aid

The Society acknowledges with appreciation the renewal of a grant of £100 from the Empire Rheumatism Council, without which it might become necessary to curtail some of the Society's activities.

Library.—The Honorary Librarian has had a complete catalogue compiled of the volumes comprising the library; this was incorporated as an inset in the Annual Report for 1954 and a new edition will appear in the Annual Report every 5 years. A classification of the books in the library to be effected during 1956 will greatly facilitate reference to volumes on particular subjects.

The Society's library of historical books on rheumatism, which is housed at the Ciba Foundation, 41 Portland Place, W.1, by permission of the Trustees, received the following additions in 1954 and 1955:

Purchased by the Heberden Society:

CARMICHAEL, R.	Observations on Sciatica and Other Neuralgic Affections. 1838.
RICHARDSON, M.	De reumatismo. 1st edition (thesis), 1826.
MUSGRAVE, G.	De arthritide anomala. Amsterdam, 1710.
WELLES, B.	A Treatise of the Gout or Joint-Evil. 1669.
MAHOMED, S. D.	Shampooing or Benefits resulting from Use of Indian Medicated Vapour Baths. 1826.
CAVERHILL, J.	A Treatise on the Cause and Cure of Gout. 1769.
ANON.	A Candid Enquiry into the Merits of Dr. Cadogan's Dissertation on the Gout. 1772.
BARTHEZ, P. J.	Traité des maladies goutteuses. Paris, 1802. Two vols.
ROBINSON, N.	An Essay on the Gout and all Gouty Affections. 1755.
PFAEHLER, J. G.	De podagra. 1733.
HEBERDEN, W.	On Education. 1818.
NENTER, G. P.	De lumbagine reumatica. 1704.
COLBATCH, J.	A Treatise of the Gout. 1697.
HAMILTON, R.	Letters on the Cause and Treatment of Gout. 1806.
LATHAM, J.	On Rheumatism and Gout (a letter to Sir G. Baker). 1796.
HOOD, W. P.	Bone-Setting and its relation to Treatment of Joints. 1871.
CORNET, C. J. B.	Méthode curative externe des douleurs rheumatismales, goutteuses. 5th edition, 1838.
COSTE	Traité pratique sur la goutte. 2nd edition, 1762.
SCUDAMORE, SIR C.	Treatise on the Nature and Cure of Gout and Rheumatism. 4th edition, 1823.
MARSILLAC, J.	La goutte radicalement guerie. 1780.
ANON.	A Treatise upon Gravel and upon Gout. 1787.

Presented by Dr. E. G. L. Bywaters:

PAULMIER, M.	Traité de la goutte. Paris, 1769.

Presented by Dr. J. Shulman:

	Lancet. Vols I and II, 1823.
BILZ	La nuova medicina naturale. (?1870-1880.)

Presented by Dr. W. S. C. Copeman:

MISAURUS, P.	The Honour of the Gout. 1735.
MACLEOD, R.	On Rheumatism. 1842.
ALTHAUS, J.	Cases of Paralysis. Rheumatism treated by Faradisation. 2nd edition, 1863.
WAGSTAFFE, J. M.	The Gouty Philosopher. 1862.

In accordance with the wishes of the Executive Committee the small balance standing to the credit of the President's Fund is being expended in the purchase of additional books, and a new fund designated "The Library Fund" has been instituted and financed by a grant of £50 from the general funds of the Society. It is much hoped that members will contribute to such a fund, as our library of books on rheumatism, arthritis and gout, printed prior to 1914, is unique. Such contributions will be gratefully acknowledged by the Committee, as would any relics associated with the Heberden family.

Several photographs of portraits of the children of Dr. William Heberden, owned by Prof. S. L. Baker (who is a direct descendant), have kindly been presented by him for the library.

OFFICERS FOR 1956

President:
Dr. Ernest Fletcher, F.R.C.P.,
41 Harley Street, London, W.1.

President-Elect:
Professor J. H. Kellgren, F.R.C.P., F.R.C.S.,
Rheumatism Research Centre, Clinical Sciences Building,
York Place, Manchester, 13.

Hon. Treasurer:
Dr. Ernest Fletcher, F.R.C.P.,
41 Harley Street, London, W.1.

Senior Hon. Secretary:
Dr. H. F. West, M.R.C.P.,
Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases, 77 Gell Street, Sheffield, 3.

Junior Hon. Secretary:
Dr. John H. H. Glyn, M.R.C.P.,
6 Southwick Place, London, W.2.

PROGRAMME FOR 1956

Clinical Meeting on February 24.
Heberden Round on June 1 and 2 at Bath.
Heberden Oration, postponed from 1955, on October 19.
Heberden Oration, 1956, Annual General Meeting, and Annual Dinner on December 14.

AUSTRALIAN RHEUMATISM COUNCIL

REPORT FOR THE YEAR 1954-1955

Office Bearers

President: His Royal Highness the Duke of Gloucester.

Executive Committee.—The following were appointed at the inaugural meeting of the Council, the last Annual Meeting, or subsequently, according to the rules:

Vice-Presidents:	President of the Royal Australasian College of Physicians, Dr. C. G. McDonald
	President of the Royal Australasian College of Surgeons, Dr. I. B. Jose (successor to Sir Harold Dew)
Chairman:	Dr. S. A. Smith
Trustees:	Mr. M. C. Alder
	Mr. Vincent Fairfax
	Mr. Alick Osborne
Hon. Secretary:	Mr. M. C. Buttfield
Other Members:	Mr. M. C. Alder
	Dr. C. R. B. Blackburn (nominee of Scientific Advisory Committee)
	Mr. Justice Herron
	Mr. E. J. Hazell
	Mr. F. P. McRae
	Dr. A. P. Murphy
Medical Director:	Dr. Selwyn Nelson (also Medical Secretary)
Hon. Auditors:	Messrs. McGrath, Nissen, and Jacombs.

Scientific Advisory Committee: The Executive Committee appointed the undermentioned:

President of the Royal Australasian College of Physicians, Dr. C. G. McDonald (*Sydney*)
President of the Royal Australasian College of Surgeons, Dr. I. B. Jose (*Adelaide*)
Dr. Mervyn Archdall (*Sydney*)
Dr. Hugh C. Barry (*Sydney*)
Dr. G. Bell (*Sydney*)
Dr. C. R. B. Blackburn (*Sydney*)
Dr. Robert Bye (*Sydney*)
Dr. P. A. Earnshaw (*Brisbane*)
Dr. Cyril Fortune (*Perth*)
Dr. John L. Grove (*Launceston*)
Sir Alexander Murphy (*Brisbane*)
Dr. A. Holmes a'Court (*Sydney*)
Dr. H. Lancaster (*Sydney*)
Dr. A. W. Morrow (*Sydney*)
Dr. Selwyn Nelson (Medical Secretary) (*Sydney*)
Dr. L. J. Parr (*Sydney*)
Dr. Ralph Reader (*Sydney*)
Dr. C. B. Sangster (*Adelaide*)
Dr. S. A. Smith (Chairman) (*Sydney*)
Dr. R. Strang (*Melbourne*)
Dr. C. J. Walters (*Sydney*)
Dr. R. Wishaw (*Hobart*).

Finance Committee.—This consists of five members as follows:

Mr. M. C. Alder (Chairman)
Mr. Vincent Fairfax
Mr. Justice Herron
Mr. F. P. McRae
Mr. Alick Osborne.

Obituary

The death of Sir Archibald Collins, of Sydney, occurred on June 24, 1955. Sir Archibald was a Foundation Member of the Council and a member of the Executive Committee and Scientific Advisory Committee since their inception. He was a fine organizer and he had looked forward to devoting a good deal of his time to the affairs of the Council. He will be greatly missed. The Chairman has conveyed the condolences of the Council to Lady Collins.

Advice was received of the death, on August 12, 1955, of Lord Horder, who had taken a major part in forming the Empire Rheumatism Council and had been its chairman until last year. The passing of Lord Horder is a loss not only to the Empire Rheumatism Council, to which the sympathy of this Council has been extended, but also to all affiliated and associated bodies.

Activities of Committees

Executive Committee.—During the year, Dr. I. B. Jose succeeded Sir Harold Dew as President of the Royal Australasian College of Surgeons. Dr. Jose has kindly accepted the offices of Vice-President of the Council and member of the Scientific Advisory Committee. Sir Harold Dew was invited to retain his membership of the council but, due to his pending retirement, he is reducing his commitments to a minimum. His plans for the future are also indefinite. He therefore tendered his resignation as a member of the council, which the committee accepted with regret but with understanding. The resignation of Dr. T. E. Lowe, of Melbourne, from

the Scientific Advisory Committee was referred to that committee and accepted. Dr. Lowe has also been asked to retain his membership of the council.

Association with the Empire Rheumatism Council has been maintained by correspondence and, in particular, by a visit to Australia during September, 1955, of the Chairman, Dr. W. S. C. Copeman. The Scientific Advisory Committee is considering the appointment of a successor to Dr. G. M. Watson as this council's representative on the Empire Rheumatism Council's Commonwealth Sub-Committee. The Ninth International Congress on Rheumatic Diseases will be held at Toronto, Ontario, Canada, from June 23 to 28, 1957, under the auspices of the Canadian Rheumatism Association.

At an Extraordinary General Meeting of the Council held in September, the rules were amended to bring the scope of the Council's activities, for taxation purposes, within the ambit of a Public Benevolent Institution; to provide for the additional office of Medical Director; to extend its powers regarding establishment of divisions; and to conform with requirements of the New South Wales Charitable Collections Act. At the same meeting a New South Wales Division was established and rules for that division were adopted. These rules were approved, also, as model rules for other divisions, when formed. It is proposed to establish further divisions when practicable.

Scientific Advisory Committee.—The educational policy of the council has been continued by inclusion of special lectures on the rheumatic diseases in post-graduate courses and to medical undergraduates.

One meeting of the Scientific Advisory Committee was held during the year. The business included a discussion of the activities of the council with special regard to the formation of divisions in the various states. The Victorian, South Australian, Tasmanian, Western Australian, and Queensland representatives of the Scientific Advisory Committee undertook to take an active part in enlisting the aid of their colleagues in their respective states with the object of forming divisions.

At the suggestion of Dr. Cyril Fortune and Dr. R. Strang, the nomination of representatives of Western Australia and Victoria to replace Dr. James Young and Dr. T. E. Lowe was deferred.

The replacement of Dr. Watson, who resigned as the representative of the council on the Empire Rheumatism Council, was left in the hands of the chairman and the medical secretary.

Formation of Australian Rheumatism Association.—Various speakers stressed the importance of a professional body to work in conjunction with the Australian Rheumatism Council and which would have the same relationship to it as that of the Heberden Society in Great Britain and the American Rheumatism Association in America to the Empire Rheumatism Council and the American Arthritis and Rheumatism Foundation, respectively.

The value of an association with the British Medical Association was also stressed. The objects of such an association would be to hold meetings of a scientific nature which would help to raise the standard of the practice of rheumatology throughout Australia. Such a body would not in any way conflict with the objects of the Australian Rheumatism Council. It was decided to seek from the Federal Council of the British Medical Association approval for the formation of the Australian Rheumatism Association. This approval was subsequently granted and the initial steps for its formation are being taken.

Visit of Dr. Copeman

Dr. W. S. C. Copeman, O.B.E., M.D., F.R.C.P., Chairman of the Empire Rheumatism Council, spent a month in Australia before leaving for New Zealand on October 4. His visit to New South Wales was sponsored jointly by the Post-Graduate Committee in Medicine in the University of Sydney and the Australian Rheumatism Council, and to other States by the Australian Post-Graduate Federation.

Dr. Copeman carried out an extensive tour of the Commonwealth of Australia. He called on the Governor-General while in Canberra and delivered a message of greeting from H.R.H. the Duke of Gloucester, President of the Empire Rheumatism Council and the Australian Rheumatism Council. He brought before Ministers of the Crown, both Federal and State, and many other influential citizens, including the Lord Mayors of Sydney and Melbourne, by whom he was tendered Civic Receptions, the importance of an organized campaign against the rheumatic diseases. He made a nation-wide broadcast in the Guest of Honour session of the Australian Broadcasting Commission. He visited hospitals and discussed the formation of new Rheumatism Clinics, and the improvement of existing ones, with the staffs of the hospitals, university departments, and, where necessary, with the Minister of Health concerned. The council has reason to believe that these actions will be effective in the improvement of the facilities for the treatment of the rheumatic diseases. He conducted courses of instruction in the rheumatic diseases, lecturing to members of the medical profession, hospital staffs, and medical students.

Not the least of his activities were discussions with the Executive Officers of the Australian Rheumatism Council. At this level he was able to pass on the experiences of the Empire Rheumatism Council in the formative steps and make many suggestions for the future development of the Council which should be of the utmost value. The Council is optimistic about the results of his visit. Already there is a quickening of interest in its work, which will be followed up vigorously. It is felt also that there is a strengthening of the ties that bind the Council with the Empire Rheumatism Council and future relations between the two bodies should be even more helpful than before.

The Council is deeply grateful to Dr. Copeman for the manner in which he devoted himself tirelessly to the cause, and to the Empire Rheumatism Council for the part it played in making the visit possible.

Ann. rheum. Dis. (1956), **15**, 193.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Influence of Rheumatic Fever on Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase. NYDICK, I., TANG, J., STOLLERMAN, G. H., WRÓBLEWSKI, F., and LADUE, J. S. (1955). *Circulation* (*N.Y.*), **12**, 795. 6 figs, 17 refs.

Glutamic oxalacetic transaminase (G.O.T.) is an enzyme present in high concentration in the cells of heart and skeletal muscle, and in the liver, kidney, and other organs. When the cells of these organs are damaged, the enzyme is released and may be found for a period in abnormal quantities in the serum. The serum enzyme content is measured spectrophotometrically by the oxidation, in the presence of malic dehydrogenase of reduced diphosphopyridine nucleotide, by the oxalacetic acid formed from a mixture of aspartic acid and α ketoglutaric acid.

At the Memorial Center for Cancer and Allied Diseases, New York, eighty patients with various grades of rheumatic fever were divided into nine groups, ranging from those with congestive heart failure and carditis to a control group with active rheumatoid arthritis alone. Correlation of the serum enzyme content was made with the erythrocyte sedimentation rate, the results of the sulphobromophthalein retention and cephalin flocculation tests, the serum alkaline phosphatase and bilirubin levels, the presence of C-reactive protein, and lastly with the findings in the left atrium of fifteen patients, as revealed at necropsy or by biopsy. (The results are given in tabular form with six case histories and six individual graphs.)

The serum enzyme levels were within normal limits in all but two of the 54 patients without active carditis, but in only nine out of the 26 patients with active or "questionably active" rheumatic carditis. However, even in patients with carditis severe enough to produce congestive failure the serum transaminase level was found to be raised on only 51 out of 267 occasions, and in an even smaller proportion of determinations in those without congestive failure. Of the fifteen cases in which the left atrium was studied histologically, there was evidence of acute inflammation in ten; in five of these the G.O.T. level was above normal. Among the remaining five patients without histological evidence of inflammation the serum enzyme level was abnormally high in only one. Liver function was normal in all but one of the eighty patients. Drugs (digitalis, mercuhydrin, and aspirin) produced no change in the serum transaminase level in non-rheumatic subjects. There was little consistent correlation in individual cases between the serum enzyme level and the clinical course or a change in the acute phase. In some cases the G.O.T. level rose when the administration of cortisone or aspirin had suppressed other serological evidence of activity. G.O.T. levels in the cerebrospinal fluid (C.S.F.) were normal in three patients with chorea. Simultaneous determination of the enzyme levels in the serum and C.S.F. in six cases showed that this was between two and five times as high in the serum, suggesting that a barrier to the free diffusion of the enzyme is present at the subarachnoid membrane.

E. G. L. Bywaters.

Effect of Intensive and Prolonged Therapy with Cortisone and Hydrocortisone in First Attacks of Rheumatic Carditis. MARKOWITZ, M., and KUTTNER, A. G. (1955). *Pediatrics*, **16**, 325. 5 refs.

The effect was studied of prolonged administration of large doses of cortisone or hydrocortisone on the incidence of residual rheumatic heart disease in patients with carditis during a first attack of rheumatic fever, with particular reference to the incidence in patients treated within 3 weeks of the onset of symptoms and those treated 3 weeks or more after the onset. To ensure an adequate series a total of forty patients was drawn from two clinics in New York and Baltimore, and the combined results are herein reported. The dosage of the drugs, which were given by mouth, was as follows:

(1) 300 mg. cortisone or hydrocortisone daily for 6 weeks, with gradual reduction over the next 3 weeks (ten patients);
(2) 300 mg. cortisone daily for 2 days, then 200 mg. daily for 40 days, followed by gradual reduction over the succeeding 3 weeks (eight patients); and
(3) the same as in (2) except that after the period

of gradual reduction a daily maintenance dose of 50 mg. cortisone was given for 2 to 10 months (22 patients).

Of 29 patients treated within 3 weeks of the onset of the illness, 24 had no evidence of heart disease when examined 6 to 22 months later, compared with only two of the eleven treated more than 3 weeks after the onset. Serious side-effects developed in eleven of the forty patients and were sufficiently severe in 4 to necessitate cessation of treatment. Hypertension was observed in eight cases, in one of which blood pressure rose to 160/120 mm. Hg and the patient had a convulsion. In four cases there was stomatitis and in one multiple paronychia. One patient became euphoric and one developed headache and became semi-conscious. In every case, however, these side-effects were temporary, and there were no permanent personality changes.

The authors suggest that cortisone in large doses should be given early in the course of rheumatic fever and continued until the disease has run its course. They consider, however, that further studies based on a larger series of cases with adequate controls are needed to establish the value of this method of treatment.

K. C. Robinson.

Erythema Marginatum. BURKE, J. B. (1955). *Arch. Dis. Childh.*, **30**, 359. 5 figs.

The literature on erythema marginatum is reviewed and nineteen cases seen at the Children's Hospital, Sheffield, and the Hospital for Sick Children, Great Ormond Street, London, are described. Of the nineteen children, aged 7 weeks to 13 years, fourteen had rheumatic fever and one had nephritis. The duration of the rash varied from a few days to 2½ months, and tended to recur. Administration of salicylates, cortisone, or ACTH did not influence the course of the condition and the appearance of the rash did not seem to be an indication of rheumatic activity.

It is considered that, although erythema marginatum and rheumatic fever are commonly associated, the former must be considered to be a non-specific phenomenon since it occurs in the absence of rheumatic fever.

Kathleen M. Lawther.

Comparison of Intramuscular Benzathine Penicillin and Oral Sulfonamide in the Control of Rheumatic Recurrences. MCCUE, C. M., GIBSON, C. D., and LINDEMANN, L. C. (1955). *J. Pediat.*, **47**, 450. 9 refs.

The recurrence rate of rheumatic fever was studied over a period of about 2 years at the Rheumatic Fever Clinic, Richmond, Virginia, in two comparable groups of patients, one group of fifty receiving 1,200,000 units benzathine penicillin intramuscularly every 28 days and the other group, also of fifty patients, receiving continuous sulphonamide prophylaxis. Of the later group 32 were given sulphadiazine, fourteen sulphafurazole ("gantrisin"), and four were lost to follow-up. Earlier investigations at this clinic revealed a recurrence rate of 61 per cent. in patients not receiving prophylactic medication. Later, a recurrence rate of 2·9 per cent. was observed in patients receiving sulphadiazine and one of 1·5 per cent. in those given sulphafurazole. In the present investigation no recurrences were observed in the group receiving benzathine penicillin, but in the group given sulphonamides there were two recurrences. The authors refer to three other favourable reports on the value of prophylactic intramuscular injections of benzathine penicillin in rheumatic fever, and conclude there is good evidence in favour of its "large-scale use in the prevention of rheumatic recurrences". *C. E. Quin.*

Rheumatic Activity in Auricular Appendages Removed at Mitral Valvoplasty. CLARK, R. M., and ANDERSON, W. (1955). *Amer. J. Path.*, **31**, 809. 7 figs, 7 refs.

At Toronto General Hospital the histological features of sections of the auricular appendage obtained at mitral valvoplasty on 78 patients with progressive cardiac failure, presumably of rheumatic origin, were compared with those of similar sections taken at necropsy in 25 control cases, the ages of the patients ranging from 17 to 53 years.

In about one-half of the 78 sections endo- and myocardial granulomata were present which consisted largely of characteristic Aschoff nodules, though some showed mononuclear cells only. Basophilia of the interstitial connective tissue was the most frequent finding. The authors state that these lesions were almost twice as frequent in patients under 31 as in older patients. There was some evidence of recent or old thrombosis, predominantly in cases of fibrillation. Only ten of the 78 sections were free from these lesions. Clinical evidence of rheumatic activity, which was not found in any of the 78 patients before operation, developed subsequently in eight.

Fibrous endocardial thickening was the only abnormality in the control specimens.

[The value of this study would have been enhanced by more details concerning the control material.] *G. Loewi.*

Potentiation of the Antirheumatic Efficacy of Sodium Salicylate by Intravenous Administration in Hypertonic Glucose Solution. (Potenziamento dell'efficacia antireumatica del salicilato di sodio mediante somministrazione endovenosa in soluzione glucosata ipertonica.) PEROSA, L., and DE VITA, P. (1955). *Rif. med.*, **69**, 1125. 17 figs.

At the University Institute of Clinical Medicine, Bari, the authors have treated fifteen patients with rheumatic fever with intravenous drip infusion of 6 to 8 g. sodium salicylate dissolved in a litre of 40 per cent. hypertonic glucose solution and given over a period of 6 to 8 hours. They claim results superior to those achieved with any other form of salicylate medication. *L. Michaelis.*

Rheumatic Fever, its Symptoms, Prevention, and Treatment. [In English.] EDSTRÖM, G. (1955). *Acta rheum. scand.*, **1**, 145. 9 figs, bibl.

Rheumatic Fever. (Das rheumatische Fieber.) KÜSTER, F. (1955). *Arch. Kinderheilk.*, **151**, 113. Bibl.

Rheumatic Fever—Diagnosis, Prophylaxis, and Therapy. SASLAW, M. S. (1955). *J. Amer. med. Ass.*, **159**, 653. 19 refs.

ossibility of Prevention of Initial and Recurrent Attacks of Rheumatic Fever. (Is het mogelijk het acuut gewrichtsrheuma, zijn verwikkelingen en zijn weder-instortingen te voorkomen.) FEROND, M. (1955). *Acta physiother. rheum. belg.*, **10**, 133.

hoice of Drugs in the Prophylaxis of Rheumatic Fever. BARROW, J. G. (1955). *J. med. Ass. Ga*, **44**, 481. 17 refs.

ome Unusual Manifestations of Rheumatic Fever. (Aspetti clinici insoliti della malattia reumatica.) MITOLO, G. R., and DOLCETTA, B. (1956). *Minerva pediat.* (*Torino*), **8**, 89. 7 figs, bibl.

reatment of Rheumatic Fever in Children with a Combination of Hormones and Salicylates. (Sul trattamento ormo-salicilico della malattia reumatica nel bambino.) CERNUSCHI, G. (1956). *Minerva pediat.* (*Torino*), **8**, 66. 15 refs.

nal Function in Children with Rheumatic Fever during Cortisone Therapy. (La funzione renale nei bambini affetti da reumatismo articolare acuto in terapia cortisonica.) CIPOLLONI, C., and PACI, A. (1956). *Minerva pediat.* (*Torino*), **8**, 57. 5 figs, 26 refs.

heumatic Fever in Infancy. A Clinical and Statistical Study of 112 Cases. (La malattia reumatica nell' infanzia. Rilievi clinico-statistici su 112 casi.) SEGAGNI, E. (1955). *Minerva pediat.* (*Torinc*), 7, 1309. Bibl.

heumatic Fever among Santiago Schoolchildren. An Analysis of 1,000 Cases and the Prevention of Exacerbations. (La enfermedad reumatica en el medio escolar de Santiago. Análisis de mil casos y prevención de las exacerbaciones.) VAISMAN, S. (1955). *Rev. med. Chile*, **83**, 455. 4 figs, bibl.

ontribution to the Geography of Rheumatic Fever in Brazil. (Contribuição à geografia da febre reumática no Brasil.) DE OLIVEIRA, P. P. (1955). *Hospital* (*Rio de J.*), **48**, 431.

revention of Rheumatic Fever in a Saskatchewan Health Region. PEACOCK, P. B. (1955). *Canad. J. publ. Hlth*, **46**, 486. 20 refs.

ffect of Prolonged Corticotropin Therapy for Rheumatic Fever on the Exchangeable Sodium Content and Body Weight. AIKAWA, J. K., and RHYNE, M. B. (1955). *Circulation* (*N.Y.*), **12**, 891. 3 figs, 13 refs.

ontinuing Military Problem of Rheumatic Fever. CARMICHAEL, D. B. (1956). *U.S. armed Forces med. J.*, **7**, 399. 4 refs.

Electrophoretic Behaviour of the Serum Glycoproteins in Acute Rheumatism Before and After Treatment. (Comportamento elettroforetico delle glicoproteine sieriche nei reumatici acuti prima e dopo terapia.) POLOSA, P., and MOTTA, L. (1955). *Reumatismo*, **7**, 350. 4 figs, 9 refs.

Diagnostic Criteria and Limits in Acute Rheumatism. (Critères et frontières de la maladie de Bouillaud.) GALMICHE, P. (1955). *Sem. Hôp., Paris*, **31**, 4123.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Comparison of Cortisone and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis. A Second Report. MEDICAL RESEARCH COUNCIL/NUFFIELD FOUNDATION JOINT COMMITTEE ON CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES (1955). *Brit. med. J.*, **2**, 695.

The methods employed in this comparative therapeutic trial of cortisone and aspirin in early rheumatoid arthritis, and the results which were obtained during its first year, have already been reported (*Brit. med. J.*, 1954, **1**, 1223; *Abstracts of World Medicine*, 1954, **16**, 405). The present report records the results obtained up to the end of the second year. Of the original 61 patients suffering from rheumatoid arthritis of not more than 9 months' duration, thirty were treated with cortisone and 31 with aspirin. During the first year three patients were lost from the trial, but during the second year no losses occurred, and all 58 remaining patients were available for assessment, thirty having been treated with cortisone and 28 with aspirin. Continuous treatment was given during the second year except in cases of remission, the dosage being left to the discretion of the physician, the aim being "to employ the minimum that would produce maximum functional efficiency and relief of symptoms without producing serious side-effects". The effect of treatment on various aspects of the disease were assessed by simple objective methods, details of which are given, and the average results in the two groups at the end of the second year are here compared with those at the end of the first:

(*a*) *Joint Tenderness.* The similarity between the results in the two groups after one year was confirmed after two years.

(*b*) *Range of Movement and Strength of Grip.* Whereas in the first year the average degree of improvement with cortisone was greater than with aspirin, after the second year the gap had narrowed, and while both groups showed some uniform deterioration, there was no significant difference between them.

(*c*) *Dexterity.* The results in the two groups remained very similar.

(*d*) *Haemoglobin Level and Erythrocyte Sedimentation Rate.* Whereas the cortisone-treated group responded better than the aspirin-treated group in the first year, this advantage was not

maintained during the second year, at the end of which the average figures for the two groups were remarkably similar.

(*e*) *Clinical Assessments.* At the end of the second year four patients in each group were reported as being in remission. The assessments of clinical activity and of functional capacity in the two groups were "more remarkable for their similarity than for their dissimilarity".

Assessment of the *x*-ray appearances of the hands, which was carried out only during the second year of treatment, was complicated by differences in the standards adopted by different observers. Although the mean gradings for osteoporosis and erosion were higher in the aspirin-treated than in the cortisone-treated group, the differences were not statistically significant. Where films taken before starting treatment were available for comparison it was found that there had been a marked, but similar, degree of progression of erosion, but not of porosis in the two groups.

In discussing the findings the authors stress the remarkable similarity which now appears between the two groups. [But it must always be remembered that the trial is being carried out on selected, and not random, groups of cases of rheumatoid arthritis.] *W. Tegner.*

Ulceration of the Skin in Rheumatoid Arthritis. [In English.] LAINE, V. A. I., and VAINIO, K. J. (1955). *Acta rheum. scand.*, **1**, 113. 3 figs, 3 refs.

Single or multiple ulceration of the skin was observed in twelve of 2,000 cases of rheumatoid arthritis seen at the Hospital of the Rheumatism Foundation, Heinola, Finland. The site of the ulcers varied but was most frequently the lower part of the leg. In all except one case the ulcers developed near an affected joint. Ulceration was preceded by oedema, and appeared to follow the breakdown of a rheumatic nodule in the skin. Peripheral vascular disease played no part in causation of this condition.

Histological examination revealed a granuloma in the dermis with perivascular exudate; there was fibrinoid degeneration of the walls of the vessels. A frequent finding was a typical rheumatic nodule at the base of the ulcer showing fibrinoid necrosis surrounded by palisading histiocytes. The ulcers, which were resistant to treatment, developed during an acute exacerbation of the rheumatoid process and subsided spontaneously during a quiescent phase. *William Hughes.*

Gold and "Acton Prolongatum" in Rheumatoid Arthritis. (Guld och acton prolongatum vid arthritis rheumatica.) SEBARDT, G. (1955). *Nord. Med.*, **54**, 1277. 12 refs.

The results obtained in a series of 1,824 patients with rheumatoid arthritis treated at Umeå Hospital, Sweden, with "Acton Prolongatum", a long-acting corticotrophin preparation, and observed for 1½ years are reported and compared with those in an earlier series of 1,086 patients treated with gold. The analysis shows that hormone therapy was, if anything, more effective than gold therapy, and the average duration of treatment shorter. Moreover, it eliminates the risk of serious complications which is associated with gold therapy. *L. Michaelis.*

Synovectomy of the Knee in Rheumatoid Arthritis. An Essay in Surgical Salvage. LONDON, P. S. (1955). *J. Bone Jt Surg.*, **37-B**, 392. 6 figs, 22 refs.

An attempt is made to assess the value of synovectomy of the knee in rheumatoid arthritis from the results obtained in 34 joints operated on since 1946. Synovectomy was considered only when accepted medical and physical treatment had failed to control the pain and swelling, and was not advised unless there was at least 45 degrees of movement and the disease had reached a relatively quiescent stage.

Usually the joint was exposed by a medial parapatellar incision dividing the quadriceps and its expansion vertically. The appearance of the joint varied considerably. A small, often semi-solid effusion was usually present. In some instances the synovial membrane was only slightly reddened and thickened, while in others it showed considerable thickening and occasionally polypoid hypertrophy. Erosion of articular cartilage was seldom marked, but the semilunar cartilages were often sufficiently diseased to require removal. The extent of the operation varied from partial synovectomy to extensive joint clearance, which in two cases included removal of the patella. Three weeks after operation the joint was manipulated under anaesthesia and active movements were begun.

Although as the result of the operation there was little change in the amount of joint movement permitted, the clinical state of most of the patients improved considerably. The late results were more favourable in joints showing little radiological change before the operation and possessing originally a good range of movement. Since it has been shown experimentally that the synovial membrane has considerable powers of regeneration, the final results may well depend upon the subsequent activity of the rheumatoid process. *Peter Ring.*

Multiple Intra-Articular Injections of Hydrocortisone in the Treatment of Rheumatoid Arthritis. (Sur les injections multiarticulaires d'hydrocortisone dans le traitement des polyarthrites chroniques évolutives.) WEISMANN-NETTER, R., KREWER, B., and LORCH, P. (1955). *Presse méd.*, **63**, 1153. 1 ref.

The authors describe their experience at the Hôpital Beaujon, Paris, with intra-articular injections of hydrocortisone acetate in the treatment of rheumatoid arthritis. Contrary to the opinion expressed by some workers that such treatment is especially suitable when only one or a few joints are affected, the authors have found the treatment particularly useful in polyarthritic cases. They describe the technique in detail. A general anaesthetic may be necessary, partly on account of the pain involved and partly because it relieves muscular spasm and makes access to the joint cavity easier. The amount injected depends on the size of the joint and degree of involvement: about 5 ml. of a solution containing 25 mg. hydrocortisone per ml. is suitable for the knee, hip, or shoulder, while 1 ml. is an appropriate dose for the distal inter

phalangeal joints. A total dose of 2 to 2·5 g. may be injected in a single case. The Thorn tests give a negative result after the injections, and there is no change in the ketosteroid or electrolyte content of the blood. This suggests that the drug is not absorbed in any quantity from the site of injection. In these circumstances the authors report a complete absence of side-effects. They find that no dietary restrictions and no control of salt intake is necessary. Similarly, the usual contra-indications for cortisone therapy can be ignored, and they have given hydrocortisone with impunity in cases complicated by active tuberculosis and peptic ulcer. Relapse, they note, is inevitable within 6 weeks to 12 months and is treated by a repetition of the injections. They underline the importance of physiotherapy as an ancillary measure, and state that in many cases the patient can dispense with the use of analgesics immediately after treatment. They do not claim that the treatment is curative, even in the most suitable type of case, but they do insist that patients who were previously crippled and bedfast have been rendered mobile and free from pain. These results, even if temporary, justify a wider use of the treatment. *William Hughes.*

Hormone Treatment of Still's Disease. (Le traitement hormonal de la maladie de Still.) MARIE, J., and SÉE, G. (1955). *Pediatrie*, **10**, 811. 21 refs.

The authors report the results obtained at the Hôpital des Enfants Malades, Paris, in the treatment with cortisone and corticotrophin (ACTH) of Still's disease in fourteen children, of whom nine developed the disease before they were 6 years old and three before they had reached their third birthday; the earliest onset was at the age of eighteen months and the latest at nine years. The joint changes were usually symmetrical, with periarticular swelling of soft tissues. Moderate anaemia and polymorphonuclear leucocytosis were frequently present, and the erythrocyte sedimentation rate and antistreptolysin titre were increased. The authors suggest that there is much in common between Still's disease, rheumatic fever, and rheumatoid arthritis of infants; in their view it is the reaction of the child's tissues to the streptococcal assault that finally determines which of the three clinical pictures will predominate.

The initial effects of hormone treatment were considerably better than the long-term effects, but on balance the results were encouraging.

Of the fourteen patients treated, three died of causes unrelated to Still's disease, two were but little improved, and contact has been lost with two others; in the remaining seven cases the results were good. It is recommended that treatment should be begun as early as possible in the disease and continued for several months. Either ACTH (50 to 100 mg. daily) or cortisone can be used, but the authors prefer the latter (by mouth) in a daily dosage of 75 mg. for children under the age of 3, 100 mg. for those between the ages of 3 and 6, and 150 mg. or more for older children, this dosage to be reduced by one-third if hydrocortisone is used, as in two cases in the present series. The dosage is halved after 30 to 60 days and thereafter reduced progressively, although in some cases a maintenance dose of 25 to 50 mg. may have to be given twice weekly for several years. Antibiotics (penicillin or aureomycin) were used in conjunction with the hormones in the authors' cases to eradicate sepsis and prevent fresh infection, but the routine administration of salicylates was found to be unnecessary. It has often been suggested that after prolonged cortisone treatment ACTH should be given to allow cortical activity to recover; the authors consider that this argument is of more theoretical than practical importance.

David Preiskel.

Lung Lesions in Rheumatoid Arthritis. ARONOFF, A., BYWATERS, E. G. L., and FEARNLEY, G. R. (1955). *Brit. med. J.*, **2**, 228. 4 figs, 26 refs.

After a brief review of reported cases of lung lesions in rheumatoid arthritis, the authors discuss their experience of such cases at the Postgraduate Medical School of London over the last 15 years.

Of 253 patients with rheumatoid arthritis, 180 were free from chest disease; in the remainder the most common lesions were bronchitis (including pneumonia), bronchitis and emphysema, emphysema alone, bronchiectasis, and old apical tuberculosis. The authors point out that these findings are not very different from those to be expected in a general hospital population.

Radiological examination of the chest in these cases and in a control series revealed that the over-all incidence of lung disease was slightly higher in patients with rheumatoid arthritis than in the controls, but that the changes in the two groups were similar. Moreover, at necropsy on 42 patients with rheumatoid arthritis no specific lung changes were found and no nodules were seen. *G. Loewi.*

Polyarthritic Hand. (Main polyarthritique.) COSTE, F. (1955). *Sem. Hôp., Paris*, **31**, 3261. 30 figs.

The writer sets out in detail the clinical, radiological, and physio-pathological appearances in polyarthritis of various types affecting the hand, with examples and illustrations, and discusses the mechanisms giving rise to the different types of resulting deformity.

The most common type may be manifest in classic form, consisting in clubbing of the wrist, M-shaped deformity of the fingers, ulnar deviation, and flexion at the metacarpo-phalangeal joints, and seen in all stages from onset to complete disorganization. In variations from this pattern the hand may be in flexion (*en griffe*), there may be radish-shaped swelling of the fingers, the distal interphalangeal joints may be chiefly affected, or there may be a combination of any of these. Complete dislocation of the finger joints, with a flaccid useless hand, develops in the variety known as arthritis mutilans, or again the thumb may show Z-shaped deformity. The changes recognized radiologically are decalcification, destruction of articular cartilage, osteophytosis, osteoporosis, and osteolysis, which may be severe.

Polyarthritis due to rheumatoid arthritis with psoriasis differs from the previous type in the absence of atrophy of periarticular structures, and sclerosing bony atrophy is not uncommon, resulting in a mummified appearance

of the fingers. Radiologically, fragmentation may be seen in old-standing cases. Further causes of polyarthritis are gonorrhoea and other infections. Distinction must be made from gout, Heberden's osteo-arthritis (in which axial deviation of the terminal phalanges is marked), and polyosteochrondritis.

The author attributes ulnar deviation to:

(1) the inert hand being held in pronation,
(2) lack of lateral support at the metacarpo-phalangeal joints,
(3) atrophy of the intrinsic muscles of the hand, thus allowing enhanced flexion and accentuating the normal tendency to ulnar deviation.

In flexion *en griffe* the proximal interphalangeal joints are affected, there is no ulnar deviation, and the tendency to flexion prevails. Theories are advanced as to the factors producing M-shaped deformity of the fingers with hyperextension of the phalanges.

Treatment includes mechanical correction of deformity in the early stages, with exercises, and later arthrodesis in suitable cases. It remains to be seen whether present-day therapy and forthcoming synthetic products more effective than cortisone and hydrocortisone may in the future prevent the development of deformity. *V. Reade.*

Treatment of Rheumatoid Arthritis with "Atebrin" [Mepacrine] and "Resochin". (Die Atebrin- und Resochin-Behandlung der progressiven Polyarthritis chronica.) ESCARPENTER-ORIOL, J., CARRERAS BAYES, A., and SARIOLS GOMEZ, M. (1955). *Medizinische*, No. 31/32, 1083. 9 refs.

At the Medical Clinic B of the University of Barcelona the authors treated fifteen patients with rheumatoid arthritis with 0·3 g. mepacrine daily until yellow coloration of the skin appeared, and then with 0·2 g. daily for 2 to 3 months.

Of the eight patients who completed the course, five seemed to improve. All suffered from gastro-intestinal symptoms.

In a further series of fourteen cases of moderately severe arthritis 500 to 750 mg. "resochin" was given daily for 10 days, then on alternate days for a further 20 days, and finally 250 to 500 mg. on alternate days for 2 to 3 months. There was some improvement in all but one case and the erythrocyte sedimentation rate tended to fall. No signs of toxicity were noted.

[No control observations are reported; therefore no conclusions should be drawn.] *G. Loewi.*

Rehabilitation of the Chronic Rheumatoid Arthritic: a Two-Year Progress Report. LOWMAN, E. W. (1955). *Arch. phys. Med.*, **36**, 431.

The effects of a programme of medical and rehabilitation treatment over a 2-year period on a selected group of 38 patients with active rheumatoid arthritis were studied at Goldwater Memorial Hospital (New York University), New York. The main criteria for selection were that the patient should be between 21 and 55 years old, with severe functional impairment, but not in obvious need of orthopaedic treatment, and with no medical contraindication for hormone therapy.

The patients' degree of incapacity was assessed according to the system of the American Rheumatism Association, the majority being placed in Classes III and IV, and also in relation to a list of over 100 activities considered necessary for self-sufficient daily living. On the basis of the latter assessment the patients were arbitrarily divided:

(1) "severely disabled" (eighteen patients),
(2) "less severely disabled" (twenty patients).

The average age in Group 1 was 46 years and average duration of the disease 13 years, the corresponding figures in Group 2 being 40 years and 7 years respectively. Treatment with cortisone or hydrocortisone was necessary "to control the activity of the rheumatic process" in 25 out of the 38 cases. Salicylates alone were sufficient for this purpose in five cases, and phenylbutazone alone in eight. [No details of the programme of rehabilitation are given, but see following abstract.]

The results were encouraging.

Of the eighteen patients in Group 1, fourteen were discharged from hospital [presumably to continue maintenance therapy] after about 11 months, seven being self-sufficient and seven partially self-sufficient at that time, and one of these was able to take a full-time job; the four remaining patients needed continued hospital care. The average improvement in functional capacity (as judged from ability to perform the activities mentioned above) was 28 per cent. in this group. The patients in Group 2 were discharged from hospital after an average stay of 7 months; fifteen were self-sufficient at that time, and seven of these were placed in full-time employment. The average functional improvement in this group was 30 per cent. *J. B. Millard.*

Total Rehabilitation of the Rheumatoid Arthritic Cripple. LOWMAN, E. W., LEE, P. R., and RUSK, H. A. (1955). *J. Amer. med. Ass.*, **158**, 1335. 8 figs, 11 refs.

The rehabilitation of patients disabled by rheumatoid arthritis is discussed with special reference to the results obtained over a recent 2-year period at the Goldwater Memorial Hospital, New York. With a combination of medical treatment and rehabilitation seven out of eighteen severely disabled patients became totally self-sufficient, one being well enough to undertake full-time employment. The average age in this group was 46 years and the average duration of the disease thirteen years. Of twenty less severely disabled patients, fifteen became totally self-sufficient, and seven of these patients were eventually placed in full-time employment. Medical treatment, when considered necessary, consisted in administration of cortisone or hydrocortisone in a dosage of 15 to 25 mg. daily at first, increased gradually to the "lowest maintenance level capable of controlling the symptoms". The duration of steroid therapy varied from 6 to 22 months, but in two cases this treatment was interrupted temporarily because of severe side-effects. In six patients relief of symptoms was obtained following a course of phenylbutazone.

Supportive psychotherapy was also employed, with

the object of counteracting passivity and dependency. Functional training in rehabilitation was directed towards "maximum performance of activities essential to independent daily living". Visits were paid to the patient's home to deal with any problems in the family situation or living conditions which might present difficulties after discharge from the protective environment of the hospital. Special apparatus was avoided except where necessary to achieve adequate function. Self-help devices included chairs and toilet seats raised above the standard height, elastic shoelaces, and long-handled shoe-horns. For reaching inaccessible parts of the room the patients had an all-purpose utility stick with multiple attachments, while for housewives there were adjustable ironing boards and work tables on casters. Splints or braces were used, especially for correction of knee-flexion deformity and for the prevention of wrist-drop and ulnar deviation of the hand. *A. Garland.*

Results of Prolonged Adrenocortical Therapy in 38 Cases of Rheumatoid Arthritis. (Résultats de la corticothérapie prolongée dans 38 cas de rhumatismes inflammatoires chroniques.) ARLET, J., RASCOL, A., and MOLE, J. (1955). *Rev. Rhum.*, **22**, 595. 1 fig., 7 refs.

The authors describe their methods of assessment and results [similar to those reported from the U.S.A. and Great Britain] in the treatment of 38 cases of rheumatoid arthritis. Only two cases did not respond to treatment with cortisone by mouth over periods from 3 to 28 months; a final maintenance dose of 25 to 87·5 mg. a day was found to be required. In no case did complications necessitate discontinuance of treatment. Gold therapy was given in addition in seventeen cases, but it was not obvious that this made any difference to the outcome. A few severe cases appear to need 75 mg. cortisone per day indefinitely; with cheaper methods of manufacture of the hormone now under way this dosage seems to be feasible. *G. S. Crockett.*

Prednisone and Prednisolone in the Treatment of Rheumatoid Arthritis. HART, F. D., CLARK, C. J. M., and GOLDING, J. R. (1955). *Lancet*, **2**, 998. 1 fig., 19 refs.

The relative efficacy of prednisone (or of prednisolone) and cortisone in the treatment of rheumatoid arthritis was assessed at the Westminster Hospital, London, from the results obtained over periods of 2 weeks to 3 months in ten patients who were transferred from cortisone to either prednisone or prednisolone and back to cortisone, and four who were transferred from prednisolone direct to cortisone. (The action of prednisone was found to be identical with that of prednisolone.) The response to treatment was assessed from the following—the patients' own estimate of pain and stiffness, finger swelling, tenderness over the proximal interphalangeal and metacarpo-phalangeal joints, erythrocyte sedimentation rate, simple function tests, and power of grip. On the whole better results were obtained with prednisone than with cortisone, most patients showing improvement in one or more of these criteria. No evidence of deterioration was found in any of the fourteen cases during prednisone therapy, but eight became worse when cortisone administration was resumed, this return of symptoms, or rebound, being marked in a few cases. At the end of the trial nine patients stated that they preferred prednisone to cortisone and five were indifferent.

The authors also describe two atypical cases of ankylosing spondylitis in which neither cortisone nor prednisone had any effect, and one case of scleroderma in which prednisolone proved as effective in controlling symptoms as five times the dosage of cortisone.

No toxic effects of prednisone were observed.

H. F. Reichenfeld.

Long-Term Treatment with Cortisone. (Traitement à long terme par la cortisone.) TOUSSAINT, J. (1955). *Rev. Rhum.*, **22**, 605.

The author describes his experience at the Hospital for Special Surgery, New York, in the treatment of 27 cases of rheumatoid arthritis and five of ankylosing spondylitis with cortisone or hydrocortisone for periods of 6 to 42 months. The effect of treatment was assessed by using Steinbrocker's method of classification. The final maintenance dose was found to be between 50 and 75 mg. per day by mouth. In about half the cases there was partial or complete cessation of activity of the disease process, even after treatment was discontinued. The long-term treatment of rheumatoid arthritis with small oral doses of cortisone seems to be gaining favour. In only one patient, in whom a peptic ulcer developed, did side-effects necessitate cessation of the treatment.

G. S. Crockett.

Diagnosis of Rheumatoid Arthritis. (Diagnostico de la artritis reumatoidea.) RUIZ MORENO, A. (1955). *Arch. argent. Reum.*, **18**, 21.

Rehabilitation of the Patient with Rheumatoid Arthritis. PRESTON, R. L. (1955). *N.Y. St. J. Med.*, **55**, 2887. 16 figs, 4 refs.

Rheumatoid Arthritis. Fifteen Years' Experience with Chrysotherapy. RAMOS, J. M. (1955). *R.I. med. J.*, **38**, 623-6 and 629. 13 refs.

Association between Silicosis and Rheumatoid Arthritis. (A propos de l'association silicose-polyarthrite.) RUELLE, M. (1955). *Rhumatologie*, 193. 13 refs.

Treatment of Rheumatoid Arthritis with Mepacrine. (Mepacrinbehandling af polyarthritis chronica.) ERLENDSSON, F. (1955). *Ugeskr. Laeg.*, **117**, 1677. 11 refs.

Nitrogen Mustard in the Treatment of Rheumatoid Arthritis. (Mostaza nitrogenada en el tratamiento de la artritis reumatoide.) ARCE GÓMEZ, E., ARTURO LOZANO, L. H. P., ORTIZ DE MONTELLANO, E., OÑATE, J., and PÉREZ DE SALAZAR, J. (1955). *Rev. med. Hosp. gen. (Mex.)*, **18**, 639. 9 refs.

Cortisone Overdosage in Rheumatoid Arthritis. Arterial and Parenchymatous Necroses; Autopsy Case Report. FINCK, P. A., (1955). *Arch. Path.* (*Chicago*), **60**, 374. 2 figs, 4 refs.

Experience with Prednisone in Rheumatoid Arthritis. (Ervaringen met prednisone bij primair chronische polyarthritis.) KUIPERS, R. K. W. (1955). *Acta physiother. rheum. belg.*, **10**, 137. 7 refs.

Personal Experience of the Effect of ACTH and Cortisone in Rheumatoid Arthritis in Children. (Eigen Ervaringen over de Invloed Van ACTH en Cortison op Reumatoide Arthritis bij Kinderen.) KUIPERS, F., EGGINK, A. A., and VAN CREVELD, S. (1956). *Ned. T. Geneesk.*, **100**, 695. 4 refs.

Electrophoresis of Proteins, Lipids, and Carbohydrates in Rheumatoid Arthritis. (Die Protein-, Lipoid-, und Kohlehydrate-lektrophorese bei der primär chronischen Polyarthritis.) SCHMID, J., PÄTZOLD, E., and FINK, R. (1955). *Wien. Z. inn. Med.*, **36**, 501. 3 figs, bibl.

Orthopaedic Management of Rheumatoid Arthritis. STEIN, I., and BELLER, M. L. (1955). *Albert Einstein med. Cent.*, **4**, 28. 3 refs.

Liver in Rheumatoid Arthritis. (Higado y artritis reumatoidea.) ALDO, L. M., and ALEJANDRO, Z. M. (1954). *Rev. méd. Valparaiso*, **7**, 391. 2 figs, 14 refs.

Liver Function Tests in Rheumatoid Arthritis. [In English.] LAINE, V., HOLOPAINEN, T., and KOSKINEN, H. M. (1955). *Acta rheum. scand.*, **1**, 184. 9 figs, 49 refs.

Protrusio Acetabuli in Rheumatoid Arthritis. MCEWEN, C., POPPEL, M. H., POKER, N., and JACOBSON, H. G. (1956). *Radiology*, **66**, 33. 7 figs, 10 refs.

(Osteo-Arthritis)

Aetiology of Osteo-Arthritis. (La etiologia de la osteoartritis.) STECHER, R. (1955). *Arch. argent. Reum.*, **18**, 79.

Osteo-Arthritis in the First Carpometacarpal Joint. An Investigation of 22 Cases. [In English.] AUNE, S. (1955). *Acta chir. scand.*, **109**, 449. 7 figs, 8 refs.

Osteo-Arthritis as a Manifestation of Certain States of Disordered Metabolism. (Espressioni osteo-artrosiche di particolari stati dismetabolici.) USSEGLIO, G., GIACOMASSO, P. P., and DEL PONTE, E. (1956). *Minerva med.* (*Torino*), **1**, 60.

Arthritis in the Elderly Patient (Osteo-Arthritis). BUNIM, J. J. (1956). *Bull. N.Y. Acad. Med.*, **32**, 102. 5 figs, 21 refs.

Arthrography of the Hip. (Arthrographies de la hanche.) COSTE, F., LAURENT, F., VERSPYCK, R., and GUILLEMINOT, R. (1955). *Rev. Rhum.*, **22**, 807. 6 figs.

Arthroses of the Wrist and Hand. (Arthroses du poignet et de la main.) WEISSENBACH, R. (1956). *Sem. Hôp., Paris*, **32**, 315. 19 refs.

(Spondylitis)

Familial Occurrence of Ankylosing Spondylitis. STECHER, R., and HERSH, A. H. (1955). *Brit. J. phys. Med.*, **18**, 176. 13 refs.

At the City Hospital (Western Reserve University), Cleveland, Ohio, the immediate relatives of 56 patients with ankylosing spondylitis were studied. Among 158 brothers and sisters, six further examples of the same condition were encountered, and among 108 parents, one was found to have the disease. This familial incidence was rather more than ten times greater than that found in a series of 616 control families. It is thought that the condition is genetically determined and is probably due to a rare autosomal dominant gene with incomplete manifestation, the penetrance being calculated as about 70 per cent. in males and 10 per cent. or slightly more in females.

[The calculations carried out to determine the "penetrance" of the gene appear to the abstractor to be of doubtful validity.] *H. Harris.*

Ankylosing Spondylitis and Fiessinger-Leroy-Reiter Syndrome: Two Aspects of the same Rheumatic Disease. (Spondylarthrite ankylosante et syndrome de N. Fiessinger-Leroy-Reiter; deux aspects de la même maladie rhumatismale.) MARCHE, J. (1955). *France méd.*, **18**, 7.

Rheumatic Spondylitis in Three Members of One Family. SELINKOFF, J. J., and MILLER, S. T. (1955). *Delaware St. med. J.*, **27**, 287. 5 figs, 21 refs.

Ankylosing Spondylitis. BAIRD, J. P. (1956). *Postgrad. med. J.*, **32**, 140. 3 figs, 35 refs.

Iritis in Ankylosing Spondylitis. WEEREKOON, L. M., and GOLDIN, C. (1955). *Ceylon med. J.*, **3**, 80. 6 refs.

Sacro-Iliac Arthritis in Ankylosing Spondylitis. (Les arthrites sacro-iliaques dans la spondylarthrite ankylosante.) HUBAULT, A. (1955). *Rhumatologie*, **189**.

Assessment of the Activity of Phenylbutazone in the Treatment of Rheumatic Fever. (Valutazione dell' attivita del fenilbutazone nel trattamento della malattia reumatica.) RATTI, G., and AMIRA, A. (1956). *Reumatismo*, **8**, 7. 23 refs.

Effect of Phenylbutazone on the Lymphocytes in Rheumatoid Arthritis. (Fenilbutazone e linfociti nell'artrite reumatoide.) GOSPODINOFF, A., and MARINO, T. (1956). *Progr. med.* (*Napoli*), **12**, 101. 1 fig., 13 refs.

Phenylbutazone in Acquired Hypoprothrombinaemia. (Butazolidina en la hipoprotrombinemia provocada.) MEYER, G., CARUSO, A. C., and BUSTAMANTE, F. F. (1955). *Arch. argent. Reum.*, **18**, 51. 1 fig.

Action of Phenylbutazone on the Coagulation of the Blood. (Accion de la butazolidina sobre la coagulacion sanguinea.) CARUSO, A. C., BUSTAMANTE, F. F., and PORTELA, C. J. (1955). *Arch. argent. Reum.*, **18**, 45. 2 figs, 3 refs.

Aldosterone: Observations on the Regulation of Sodium and Potassium Balance. LUETSCHER, J. A., and CURTIS, R. H. (1955). *Ann. intern. Med.*, **43**, 658. 4 figs, 21 refs.

Test to distinguish Functional from Organic Limitation of Movement in Spine or Hip. AIRD, I. (1955). *Brit. med. J.*, **2**, 1110. 6 figs.

Recurrent Retinal Haemorrhages in Systemic Disease similar to Fiessinger-Leroy-Reiter's Syndrome. [In French.] SPIRA, C. (1954). *Bull. Soc. Ophtal. Fr.*, No. 1, 129.

(Miscellaneous)

Insulin Shock in the Treatment of Articular Rheumatism. (Der Insulinstoss in der Behandlung des Gelenkrheumatismus.) BRÜHL, W., and JAHN, H. J. (1955). *Dtsch. med. Wschr.*, **80**, 1727. 29 refs.

The effects of insulin shock in the treatment of rheumatoid arthritis are explained on the basis of Selye's adaptation syndrome, the hypoglycaemia produced by the insulin being considered to act as the stress which causes the production of adrenaline. This effect has been taken advantage of in the treatment of various allergic diseases, such as bronchial asthma and eczema.

The authors, writing from the City Hospital, Korbach, Germany, describe the results of using this method in the treatment of fourteen patients, thirteen with chronic rheumatoid arthritis and one with ankylosing spondylitis. The usual procedure consisted of an intravenous injection of 10 to 15 units insulin given in the morning, but in a few cases 12 to 20 units were given subcutaneously in the morning and repeated 4 hours after the midday meal.

In eight patients there was lasting subjective and objective improvement, as shown by the disappearance of pain and an increase in the range of joint movement.

In three others the improvement was transient, lasting only during active insulin therapy.

The best results were achieved when there was a rapid fall in blood sugar content.

It is considered that the over-all results were as good as those achieved with cortisone.

The simultaneous injection of glucose along with the insulin annulled any beneficial effects; the subcutaneous injection of adrenaline gave results similar to those of insulin, but marked tachycardia and a feeling of anxiety prevented repeated administration.

It is suggested that the stimulation of adrenaline secretion provoked by the hypoglycaemia causes stimulation of the sympathetic nervous system and of the hypophysis, resulting in increased secretion of ACTH and the production of glucocorticoids.

P. I. Reed.

"Multifidus Triangle" Syndrome as a Cause of Recurrent Low Back Pain. BAUWENS, P., and COYER, A. B. (1955). *Brit. med. J.*, **2**, 1306. 1 fig., 5 refs.

One form of lumbar pain is attributed to the "multifidus triangle" syndrome described by Livingston in 1941, which may come on after physical exertion involving bending or twisting the spine. A sharp localized pain in the low back is followed by a chronic ache in the lower part of the multifidus muscle; the acute pain tends to recur. Examination of patients suffering from this type of pain reveals a local point of tenderness, pressure on which causes radiation of the pain. The treatment given by Livingston consisted in local injections of 2 per cent. procaine into the trigger area. The authors report twenty cases seen at St. Thomas's Hospital, London, in which pain was aggravated by lumbar extension and in all of which a trigger area of local tenderness could be found in the multifidus triangle. Straight leg raising was not painful and there was no radiological abnormality in any of these cases. A mixture of hydrocortisone, hyaluronidase, and procaine was injected into the trigger area. Improvement was observed in all cases, although a second injection was required in two. At the end of 4 weeks all the patients were free from symptoms.

W. Tegner.

Antirheumatic Potency of Butazolidin in Low Doses. KELLY, M. (1955), *Brit. J. phys. Med.*, **18**, 191. 2 figs., 7 refs.

The author gives his personal experience with phenylbutazone ("Butazolidin") in the treatment of 800 patients with various rheumatic conditions over a period of 3 years. He considers it to be a specifically antirheumatic drug which is not dangerous if given in correct dosage to suitable patients. Patients over the age of 65 and those with chronic diseases of the blood, kidneys, cardiovascular system, or alimentary tract should be excluded. He recommends that a dose of 0·6 g. should not be given for more than 2 days at a time and 0·4 g. for not more than a week, and states that 0·2 or 0·3 g. is usually a sufficient maintenance dose. The toxic effects, if any, nearly always occur during the first 4 weeks of treatment, and the patient should be instructed to watch for them and told to stop the drug if any occur. Patients who receive no benefit from the drug at first may respond to a second or third trial.

The author stresses that phenylbutazone is not an analgesic, but is specifically anti-rheumatic in action, the mechanism whereby it suppresses rheumatic inflammation remaining unknown.

Oswald Savage.

Toxic Effects of Phenylbutazone (Butazolidin): Review of the Literature and Report of the 23rd Death following Its Use. MAUER, E. F. (1955). *New Engl. J. Med.*, **253**, 404. 2 figs, bib.

Electrocardiographic Changes in Reiter's Syndrome. MAYNE, G. O. (1955). *Brit. J. vener. Dis.*, **31**, 238. 2 figs, 14 refs.

Two cases of gonorrhoea complicated by Reiter's syndrome showed electrocardiographic changes without any clinical cardiovascular abnormality.

P. D. Trevor-Roper.

Two People of the Same Family with Ophthalmic Migraine and Dupuytren's Disease. Good Influence of α-Tocepherol. [In French.] HENRY, C. (1954). *Bull. Soc. Ophthal. Fr.*, No. 1, 93.

Humoral Changes in Articular Rheumatism. (Über humorale Veränderungen beim Gelenkrheumatismus.) VOIT, K. (1955). *Med. Klin.*, **50**, 1849. 20 refs.

Electro-Encephalogram in Chronic Rheumatism. (L'elettroencefalogramma nel reumatismo cronico.) LUCHERINI, T., NATALE, P. and TUZI, T. (1955). *Reumatismo*, **7**, 344. 2 figs, 38 refs.

Psychosomatic Medicine in Resistant Scapulo-Humeral Periarteritis. (Péri-arthrites scapulo-humerales rebelles et médecine psychosomatique.) BERTIN, LASSELIN, and WAGHEMACKER (1955). *Rhumatologie*, **184**.

Diagnosis of So-Called Scapulo-Humeral Periarthritis. (Die Diagnose der sogenannten Periarthritis humeroscapularis.) KOLDE, H. (1955). *Dtsch. med. Wschr.*, **80**, 1844.

Depot Salicylate in the Treatment of Rheumatism. (Depot-Salicylat in der Rheumatherapie.) DÖRFLER, F. (1955). *Med. Klin.*, **50**, 2114. 1 fig, 1 ref.

Palindromic Rheumatism. A Clinical Description and an Electrophoretic Analysis of the Synovial Fluid. [In English.] WIRTSCHAFTER, Z. T., WILLIAMS, D. W., and GAULDEN, E. C. (1955). *Acta med. scand.*, **153**, 119. 3 figs, 15 refs.

Cutaneo-Articular Syndromes. (Síndromes cutáneo-articulares.) VILANOVA, X., PIÑOL, J., and DE DALMASES GOSÉ, R. (1955). *Rev. esp. Reum.*, **6**, 169. 5 figs.

Rheumatoid Arthritis and Spondylitis. The Clinical History and the Pathological Changes after 20 Years of Disability. GILMORE, H. R., and STECHER, R. M. (1955). *Milit. Med.*, **117**, 432. 6 figs.

History-Taking in Rheumatic Disorders. (Cómo orientar el interrogatorio de los enfermos reumáticos.) SANS SOLÁ, L. (1955). *Rev. esp. Reum.*, **6**, 154.

Focal Infection in Rheumatology. (Considerações sôbre infecção focal em reumatologia.) VILLELA NUNES, C. (1955). *Med. Cirurg. Farm*, No. **233**, 402. 24 refs.

Dental Aspects of Rheumatism. (Aspectos dentales y reumaticos.) CHAIT, B. (1955). *Rev. argent. Reum.*, **20**, 155.

Hereditary Factors in Rheumatism. (La herencia en reumatismo.) STECHER, R. (1955). *Arch. argent. Reum.*, **18**, 11.

Combination of Drugs [Phenylbutazone, Salicylamide, and Codeine Phosphate] Useful in Rheumatism. (Una asociacion medicamentosa util en el reumatismo.) RUIZ MORENO, A., LITTER, M., and TORINO, A. (1955). *Arch. argent. Reum.*, **18**, 37, 22 refs.

Practical Value of Serological Reactions in Rheumatism. (De Praktische Waarde van de Serologische Reumareacties.) HOLLEMAN, E. J. W. (1956). *Ned. T. Geneesk.*, **100**, 700. 17 refs.

Skin Reaction to the Local Application of the Tetrahydrofurfurylic Ester of Nicotinic Acid as a Test for the Activity of Rheumatic Disease. (La reazione cutanea all'applicazione topica di estere tetraidrofurfurylico dell'acido nicotinico quale test di attività dell'infezione reumatica.) GIULIANI, V. (1956). *Rif. med.*, **70**, 257. 4 refs.

Problems of the Functional Re-education of Rheumatic Subjects. (Il problema della rieducazione funzionale dei reumatici.) MASTURZO, A. (1956). *Reumatismo*, **8**, 28. 2 figs, bib.

Purpura Rheumatica: a Type of Allergic Cutaneous Arteriolitis. RUITER, M. (1956). *Brit. J. Derm.*, **68**, 16. 1 fig., 5 refs.

Treatment of Rheumatoid Arthritis and Osteo-Arthritis with Succinate-Salicylate. GILPIN, W. A. (1955). *J. Mich. med. Soc.*, **54**, 1428. 30 refs.

Chronic Rheumatic Disease. Clinical Evaluation of a Topical Methyl Salicylate Compound. BRUSCH, C. A., GRASSE, L. A., PAPAS, P. N., and LAMPHIER, T. A. (1956). *Maryland med. J.*, **5**, 36. 2 refs.

Amidopyrine Gentisate in the Treatment of Rheumatism. (Il gentisato di amidopirina nella terapia del reumatismo.) ANDRES, G., and FARINELLA, A. (1956). *Minerva med.* (*Torino*), **1**, 50. 6 refs.

Clinical Observation on the Therapeutic Action of a New Antirheumatic Preparation "Linidox". (Osservazioni cliniche sull'azione terapeutica di un nuovo preparato antireumatico: il Linidox.) NOFERI, G. (1956). *Minerva med.* (*Torino*), **1**, 52. 2 refs.

Certain "Rheumatic" Conditions treated with Thiodiglycol. (Quelques affections "rhumatismales" traitées par le thiodyglycol.) COULON, R. (1956). *Scalpel* (*Brux.*), **109**, 123. 12 refs.

Measurement of Prevalence of Arthritis and Rheumatism from Interview Data. COBB, S., THOMPSON, D. J., ROSENBAUM, J., WARREN, J. E., and MERCHANT, W. R. (1956). *J. chron. Dis.*, **3**, 134-139. 1 fig., 5 refs.

Aetiology, Pathogenesis and Classification of Periarthritis of the Shoulder. (Considérations sur l'étiopathogenie et la classification des périarthrites de l'épaule.) ROBECCHI, A. (1955). *Rev. Rhum.*, **22**, 813.

Gout

Complete Relief of Gout. MARSON, F. G. W. (1955). *Lancet*, **2**, 360. 3 figs, 9 refs.

The effective control of chronic gouty arthritis in seven cases treated for long periods with sodium salicylate or with probenecid is reported from the University of Leeds. The cases, selected from a larger series, had been under observation for at least 18 months and in each the blood urea level was normal. No dietary or alcoholic restriction was imposed and apart from a high fluid intake treatment consisted in administration of either sodium salicylate in a dosage of 30 grains (2 g.) three times a day or probenecid in a dosage of 0·5 g. four times a day. Colchicine was given when acute attacks occurred.

In all cases there was relief of chronic symptoms after intervals of 2 to 21 months from the start of treatment, with cessation of pain, reduction in swelling, and healing of ulcers. Acute episodes ceased in all cases although in one they continued for the first 33 months of treatment. The duration of remission from an acute attack varied between 6 and 43 months. Probenecid, which was given to patients who were sensitive to salicylates, was found less effective as a uricosuric agent than sodium salicylate. In one case it failed to prevent chronic gouty symptoms which had previously been controlled by salicylates, but in others it was of value. The author suggests that it is indicated in patients who cannot tolerate salicylate. *Charles Rolland.*

Clearance of Uric Acid in Normal and Gouty Subjects. (La clearance dell'acido urico nel soggetto normale e nel gottoso.) SALA, G., BALLABIO, C. B., and AMIRA, A. (1955). *Reumatismo*, **7**, 223. 22 refs.

At the Medical Clinic of the University of Milan the authors investigated the renal function in regard to uric acid of thirty healthy and nine hyperuricaemic gouty subjects. The uric acid clearance was determined and at the same time the glomerular filtration rate was estimated by the endogenous creatinine method and the sodium thiosulphate method.

Their results provide support for the hypothesis that a renal factor is involved in the pathogenesis of hyperuricaemia in gout. The mean value for uric acid clearance in the normal subjects was $9{\cdot}25 \pm 0{\cdot}75$ ml. per minute, and in the gouty subjects $3{\cdot}59 \pm 0{\cdot}3$ ml. per minute, the difference being highly significant statistically. A relationship was observed between uric acid clearance and urinary flow, the former decreasing even in normal subjects when the latter was less than 1 ml. per minute.

In four gouty subjects there was a marked reduction in the glomerular filtration rate; the mean uric acid clearance in these cases was $3{\cdot}40 \pm 0{\cdot}44$ ml. per minute, whereas in the remainder it was $3{\cdot}87 \pm 0{\cdot}43$ ml. per minute. *E. Forrai.*

Some Observations on 520 Gouty Patients. KUZELL, W. C., SCHAFFARZICK, R. W., NAUGLER, W. E., KOETS, P., MANKLE, E. A., BROWN, B., and CHAMPLIN, B. (1955). *J. Chron. Dis.*, **2**, 645. 7 figs, 20 refs.

A clinical analysis of 504 examples of primary and sixteen of secondary gout has been made. The group included 373 males and 131 females with primary gout. Visible tophi were present in 13 per cent. of males and 3·8 per cent. of females. Initial serum uric acid determinations were below 6 mg. per 100 ml. in 27·5 per cent. of males and in 41 per cent. of females. These determinations were often made following medication with uricosuric agents. Comparison of colorimetric and enzymatic (uricase) estimations of serum uric acid revealed no practical advantage in favour of the latter. The coincidence of other diseases is recorded. The cause of death in eighteen gouty patients is reported. Alcoholism and uraemia were observed much less frequently than is commonly presumed. Special laboratory investigations in a few of these patients included "atherogenic indices" which were generally elevated. Serum glutamine and glutathione were all within normal range.

For treatment of acute gouty arthritis, effective agents include colchicine, corticotropin, demecolcine, and phenylbutazone. As an adjunct measure the local injection of hydrocortisone was valuable. Less effective and often actually aggravating were oral cortisone, hydrocortisone, and "metacortandracin" [prednisone]. In the management of chronic gouty arthritis phenylbutazone and probenecid, singly or in combination, appear to be of greatest merit. Of the currently available antigout agents phenylbutazone is the single most effective remedy, valuable at once in termination of acute gouty arthritis, prevention of acute exacerbations, and control of chronic gouty arthritis. The undesirable side effects of chronic gouty arthritis.—[*Authors' summary.*]

Desacetylmethylcolchicine in Acute Gouty Arthritis. COLSKY, J., WALLACE, S., and BANOWITCH, M. M. (1955). *New Engl. J. Med.*, **253**, 730. 16 refs.

Desacetylmethylcolchicine, an alkaloid chemically similar in structure to colchicine, was tried at Maimonides Hospital, Brooklyn, N.Y., in the treatment of ten patients suffering from acute gout. The drug was given by mouth to a total dose of 5 to 8 mg., most of the patients receiving 1 mg. an hour for 5 to 8 hours. Pain was relieved in 8 to 24 hours, but joint swelling subsided more slowly. No significant change was observed in the leucocyte count or in the blood uric acid level. In one case the condition relapsed after an interval of several days, but a second course of the drug was followed by symptomatic relief. Side-reactions were transient and minimal. One patient had a maculopapular rash while another complained of slight loss of appetite. No gastro-intestinal disturbances were ob-

served even in those patients who had experienced attacks of nausea, vomiting, or diarrhoea during treatment with colchicine.

On the basis of these findings and the results of experiments on animals the authors conclude that the relatively non-toxic desacetylmethylcolchicine is preferable to colchicine in the treatment of acute gouty arthritis.

A. Garland.

Effect of Intravenous Demecolcine (Colcemid) on Acute Gout. KUZELL, W. C., SCHAFFARZICK, R. W., and NAUGLER, W. E. (1955). *Arch. intern. Med.*, **96**, 153. 7 refs.

Demecolcine ("Colcemid"), an alkaloid from the meadow saffron, differing from colchicine structurally in the replacement of the acetyl by a methyl radical, was given intravenously to a series of twenty patients with acute gout.

Of the twenty patients, fifteen enjoyed complete remission within 48 hours after the administration of 1 to 4 mg. demecolcine. Four other subjects were afforded partial amelioration of signs and symptoms. The only undesirable side-action was the occurrence of diarrhoea in two of the twenty patients.—[*Authors' summary.*]

Pararheumatic (Collagen) Diseases

Relation between Periarteritis Nodosa, Other Nodular Forms of Arteritis, and the Collagen Diseases. (Rapports entre la périartérite noueuse, les autres artérites nodulaires et les maladies du collagène.) HABIB, R. (1955). *Ann. Méd.*, **56**, 496. 13 figs, bibl.

This paper contains a long critical review of the experimental, clinical, and histological evidence of the relationship between periarteritis nodosa and other diseases producing a similar pathological picture. The author supports her interpretation of the literature with a few cases of her own and the reproduction of some excellent photomicrographs.

She reaches the conclusion that periarteritis nodosa is a distinct entity and can be distinguished by a number of criteria from other disorders, several characteristics of which it may share:

(1) From other necrotizing arteritides in allergic aetiology it can be distinguished by the fact that of these only the smaller vessels, which may include veins as well as arteries, are affected, and by the fact that all lesions are manifestly of the same age, whereas in periarteritis nodosa different phases of the disease process are found at the same time.

(2) The relationship of periarteritis nodosa to malignant hypertension is discussed at some length.

Both types of lesion have frequently been reported to occur in the same patient, and the question has been raised whether a periarteritis affecting the kidneys could give rise to hypertension as a result of renal ischaemia, or whether a pre-existing hypertension could be responsible for the development of periarteritis nodosa. It is noted that many cases of periarteritis nodosa, especially in the young, present as malignant hypertension.

The author reaches the conclusion that the histological appearance of the kidneys in cases of malignant hypertension differs in many essentials from that seen in periarteritis nodosa, for example, in the smaller diameter of the affected vessels (less than 100μ), in the fact that only 5 to 10 per cent. of the glomeruli show the classic changes of fibrinoid degeneration, and lastly in the absence of the rupture of the internal elastic membrane, which is so typical of periarteritis nodosa.

In spite of some overlapping, periarteritis nodosa can also be distinguished from the collagen diseases when all the evidence, clinical as well as pathological, is considered. Thus, it may be differentiated:

(1) from rheumatic carditis, again by the size of the vessels affected, and by the presence of Aschoff bodies and the fibrosis seen in old rheumatic lesions, as against the complete disintegration of the vessel wall typical of periarteritis nodosa;

(2) from dermatomyositis, by the primary affection of the muscle fibres in this condition as compared with their secondary destruction in periarteritis nodosa—a photomicrograph of a muscle biopsy specimen taken on the eighth day of the illness from a case of dermatomyositis already shows considerable degeneration of the muscle fibres—and again by the absence of the complete disintegration of the vessel wall, such as is seen in periarteritis nodosa;

(3) from scleroderma by the predominance of the skin lesions and by the hypertrophy of the muscularis and intima of the blood vessels; and finally

(4) from disseminated lupus erythematosus by the presence of the L.E. cell, haematoxylin bodies, and the L.E. factor.

[This is an excellent paper, concisely written and closely argued, and would well repay reading in the original.]

H. F. Reichenfeld.

The Significance of a Positive L.E. Phenomenon. WEISS, R. S., and SWIFT, S. (1955). *Arch. Derm. (Chicago)*, **72**, 103. 24 figs, 33 refs.

The specificity of the L.E.-cell phenomenon was studied at Washington University, St. Louis, Missouri, two techniques being used which gave identical results—namely, the two-hour clot technique and that of Barnes and Moffatt in which suspect serum is added to a normal buffy coat. No L.E. cells were found in blood specimens from 24 patients suffering from penicillin reactions, but they were present in three out of sixteen from patients receiving hydrallazine who had developed some symptoms attributed to the drug. In the course of the study cells were seen in which the ingested body had retained a sharp outline but in which there was no remaining chromatin pattern. These cells, which the authors term "advanced tart cells", were observed in acute and subacute disseminated lupus erethymatosus, in rheumatoid arthritis, and in the hydrallazine syndrome. As true L.E. cells were sometimes seen in later preparations from the same patients these cells are regarded as precursors of some L.E. cells.

In preparations from 350 patients with a variety of other diseases no L.E. cells were found. *E. G. Rees.*

Corticotrophin and Cortisone in the Treatment of Scleroderma. ZION, M. M., GOLDBERG, B., and SUZMAN, M. M. (1955). *Quart. J. Med.*, **24**, 215. 2 figs, 11 refs.

Cortisone and corticotrophin were given at Johannesburg General Hospital, South Africa, to fourteen patients (seven females and seven males) suffering from scleroderma. Striking improvement was obtained in four patients and slight improvement in nine, in one patient no subjective or objective change was observed. In one case there was clinical and histological reversal to normal. The duration of the disease appeared to influence the results since none of the patients with symptoms of more than six months' duration derived much benefit. The best results were obtained in patients without any peripheral vascular disturbance: nine of the ten patients in whom there was little or no response suffered from Raynaud's disease. Improvement was not maintained when treatment was temporarily discontinued. No difference was observed between the response to cortisone and that to corticotrophin. *E. W. Prosser Thomas.*

Periarteritis Nodosa limited to the Pulmonary Circulation. BRAUNSTEIN, H. (1955). *Amer. J. Path.*, **31**, 837. 8 figs, 44 refs.

True periarteritis nodosa, which the authors distinguish from necrotizing angiitis due to hypersensitivity, rarely affects the pulmonary arteries. In the present paper six cases are described in which the disease was limited to the lungs, the systemic arteries being free. In all six cases the condition was associated with prolonged pulmonary hypertension, which was also present in all those cases previously reported in the literature in which the diagnosis was acceptable by the author's standards. A pathogenetic relationship is therefore suggested.

D. M. Pryce.

Role of ACTH and Cortisone in the Treatment of Systemic Lupus Erythematosus. HARRIS-JONES, J. N. (1956). *Postgrad. med. J.*, **32**, 145. 1 fig, 16 refs.

General Pathology

Studies in Rheumatic Fever. I. The Clinical Significance of the Aschoff Body based on Morphologic Observations. II. Origin of Cardiac Giant Cells. TEDESCHI, C. G., WAGNER, B. M., and PANI, K. C. (1955). *Arch. Path.* (*Chicago*), **60**, 408-422 and 423-430. 23 figs, 39 refs.

In the first part of this paper the authors describe an extensive study of the histology of the Aschoff nodule carried out at Hahnemann Medical College, Philadelphia, in order to determine whether its presence or appearance offers a basis for correlation with the course of rheumatic heart disease. The Aschoff body has generally been regarded as pathognomic of the disease and to be a specific granulomatous inflammation, analogous to the tubercle in tuberculosis. A total of 400 biopsy specimens of the left auricular appendage removed during the course of operation on the mitral valve were examined. post-mortem examination in 22 cases having indicated that the histology of the auricular appendage is representative of the heart as a whole. All the cases had been diagnosed on clinical and laboratory grounds as "inactive cases of mitral valvular disease of rheumatic origin". The study showed that the Aschoff body undergoes a series of histological changes roughly divisible into three stages, a preliminary exudative phase, a proliferative phase, and finally, during the stage of healing, a senescent phase. Extensive details of these changes both in the cellular and organized constituents as well as in the ground substances are recorded and illustrated.

The 400 cases were then classified into two main categories:

(1) active rheumatic carditis and
(2) healed or healing rheumatic carditis, disregarding the presence of mural thrombosis.

Only 2 per cent. of all the cases showed Aschoff bodies representative of active disease and 17 per cent. nodule of the healing, healed, or senescent type. Thus in 81 per cent. the tissue biopsy could not substantiate the clinical diagnosis, but it did not invalidate it "inasmuch as fibrosis and scarring represent the end-result of the primary collagen injury". The "histologically active" cases did not show any increase in operative morbidity or mortality, as might have been expected, but as the authors point out they were perhaps protected by the widespread use of potent steroid hormones and antibiotics. Some cases showed both types of nodule and were considered to be cases of reactivation of an old carditis. It is concluded that the Aschoff body is not a reliable exponent of rheumatic activity. Of the other tests of activity, only the erythrocyte sedimentation rate appeared to correlate with the tissue changes.

There has been much controversy regarding the multinucleated large cell which characterizes the Aschoff body, and in the second part of this paper [by the two first-named authors only] histological evidence is presented which suggests that there are two distinct types of cardiac giant cell: on the one hand, a true Aschoff giant cell which is derived from the Anitschkow myocyte and is considered to be a cardiac histiocyte mobilized in response to the primary rheumatic damage to collagen fibres and ground substance; on the other hand myocardial damage can occur in a number of other conditions (although this general group includes rheumatic myocardial degeneration), and as a result of this giant cells may develop from the nuclei of sarcolemma in an attempt at muscle regeneration. The minute histological differences between these two types of giant cell are described. *Harry Coke.*

Clinical Experience with the C-Reactive Protein Test. ROANTREE, R. J., and RANTZ, L. A. (1955). *Arch. intern. Med.*, **96**, 674. 1 fig, 24 refs.

The authors have made an evaluation of the usefulness of determination of the presence of C-reactive protein in the serum, based on its estimation at Stanford University School of Medicine, San Francisco, in 443 cases of a wide range of medical conditions and in fifty healthy control subjects. Modern developments in the introduction of a specific antiserum for this protein

renders the test simple and readily available as a diagnostic aid. The C-reactive protein is not known to occur in normal human serum, but readily develops as early as 14 to 26 hours after inflammation or tissue injury. The test for its presence has been claimed to be a sensitive guide to the activity of rheumatic fever, the substance disappearing with the suppression of clinical signs and symptoms; its appearance or disappearance is also said to precede corresponding changes in the erythrocyte sedimentation rate (E.S.R.). In the present study the result of the test was correlated with that of the E.S.R., the leucocyte count, and temperature in each instance. Each case was minutely studied for the presence of one or more sources of tissue destruction, and in a number the findings were confirmed at necropsy.

In the group of fifty healthy controls only two positive results were obtained, and these became negative soon afterwards. One of these patients had just undergone a dental extraction and the other was suffering from a severe local immunization reaction. Of 26 psychoneurotic patients, the test result was negative in all, while two positive results were obtained among fourteen cases in which no organic disease could be discovered. In bacterial infections the presence of C-reactive protein was considered to be a more sensitive index of infection than other methods, but viral infections did not result in so consistent or copious a production of the protein; this applied also, in some part, to tuberculous infections, in which the E.S.R. was more reliable. The results of the test in patients with bacterial infections, active rheumatic fever, acute myocardial infarction, and widespread malignant disease were consistently positive, an exception being noted in two out of ten cases of rheumatoid arthritis in which they were negative; in these, however, the disease, although definitely active, was mild in degree. In a number of other disease conditions, for which the results are briefly reported, the reaction was in most cases negative. *Harry Coke.*

Auto-Antibodies in Rheumatoid Arthritis. (Auto-anticuerpos en la poliartritis crónica progresiva.) Foz, A., and Batalla, E. (1955). *Rev. esp. Reum.*, **6**, 142.

Working at the Municipal Hospital for Infectious Diseases, Barcelona, the authors have devised a test for rheumatoid arthritis which gave a positive result in 24 out of 32 patients with the disease, and a negative result in 140 out of 144 control subjects. In this test, which is claimed to be more specific and more sensitive than the Waaler-Rose test, the serum to be tested is added in varying dilutions to a suspension of *Brucella* which has been "sensitized" by incubation for one hour at 37° C. with serum from a patient with brucellosis. The serum chosen for this purpose is one poor in complete (agglutinating) antibodies and rich in incomplete antibodies against *Brucella*, the globulins containing these antibodies being adsorbed by the organism in the suspension. The addition of serum from a case of rheumatoid arthritis then causes agglutination of the brucellae owing to its content of antibodies to human globulin. Control tests are carried out with non-sensitized suspensions. *L. Michaelis.*

Variations of Beta Glucuronidase Concentration in Abnormal Human Synovial Fluid. Jacox, R. F., and Feldmahn, A. (1955). *J. clin. Invest.*, **34**, 263. 2 figs, 6 refs.

The importance in mucin metabolism in the enzyme β-glucuronidase, which splits conjugated glucuronides, prompted the present study, reported from the University of Rochester, New York, of the concentration of the enzyme in synovial fluid. Using a modification of the method of glucuronidase assay described by Talalay and others (*J. biol. Chem.*, 1946, **166**, 757), the authors estimated the enzyme content of fluid from joints affected by a variety of pathological conditions in 56 cases. They found a very high concentration in synovial fluid from patients suffering from pyogenic arthritis, a moderate yield in some cases of rheumatoid arthritis, and a low yield in cases of degenerative arthritis. Synovial fluid with a high cell content tended to have a high β-glucuronidase content, but the correlation was not absolutely linear. The concentration of the enzyme was reduced after removal of the cells by centrifugation and, although synovial secretion cannot be excluded, the enzyme is probably derived from disintegrated leucocytes.

In three cases, one of pyogenic, one of rheumatoid, and one of degenerative arthritis, serial determinations of the β-glucuronidase content of the synovial fluid were made. The level was very high in the initial phase in the case of pyogenic arthritis and subsequently appeared to vary with the degree of activity. Similarly in the case of rheumatoid arthritis there was a high correlation between the enzyme content and the clinical assessment of activity. In the case of degenerative joint disease the initial level was low and no appreciable change was observed over a period of study of 170 days. The estimation of the β-glucuronidase content of the synovial fluid would not appear to have any specific diagnostic value, but it appears to reflect the cellular response to the inflammatory change in the synovial membrane and, once the diagnosis is made in cases of rheumatoid arthritis, serial determinations might afford a possible guide to changes in the degree of activity. *R. E. Tunbridge.*

Non-Antigenicity of Chondroitin Sulphate. Boake, W. C., and Muir, H. (1955). *Lancet*, **2**, 1222. 13 refs.

An attempt was made at St. Mary's Hospital, London, to produce experimental arthritis in rabbits by injecting a heat-killed vaccine prepared by incubating rabbit chondroitin sulphate with β-haemolytic streptococci, and to determine whether this procedure led to the production of auto-antibodies to chondroitin. Glynn and Holborow (*Lancet*, 1952, **2**, 449) produced arthritis in rabbits by injecting a similar vaccine prepared from human chondroitin sulphate, but the present authors considered it necessary to use a substance from an animal of the same species for the demonstration of auto-antibody production.

A group of twelve rabbits were given intravenous injections of the vaccine three times a week for 2 weeks, followed by a booster dose after another 2 weeks. Control groups of six rabbits received similar injections

of chondroitin sulphate only and of heat-killed streptococci only.

In none of the three groups of animals could antibodies to chondroitin sulphate be demonstrated in the serum, and no rabbit developed arthritis. It is thought possible that the positive results obtained previously may have been due to a sensitization reaction to traces of protein in the chondroitin preparation. *G. W. Csonka.*

Electrophoretic Patterns of Plasma Proteins in Cases of Non-Specific Infective and Rheumatic Polyarthritis during Treatment with Mud Packs. [In Russian.] CHULKOV, E. G. (1955). *Ter. Arkh.*, **27**, 29, No. 6. 4 figs, 6 refs.

In 43 polyarthritic patients undergoing treatment with mud packs at the Crimean Medical Institute the plasma proteins were repeatedly analysed by means of quantitative paper chromatography.

A general tendency towards the restoration of a normal pattern was observed to run parallel with the considerable clinical improvement. The plasma albumin content tended to rise from the commonly observed low levels, whereas the gamma globulin level tended to recede from high to normal values. However, during the "balneo-reaction" the plasma protein patterns underwent changes in the opposite direction, the albumin content falling and that of gamma globulin rising; similar changes occurred in some cases also towards the end of the course of treatment, and these are explained by the so-called "pessimal" reaction (Vvedenskii), or the "protective inhibition" of Pavlov. It is concluded that plasma protein chromatography affords a valuable method of estimating the effectiveness of this type of treatment. *A. Swan.*

Determination of Capillary Fragility in the Conjunctiva in Health, Disorders of the Circulation, Hypertension, Rheumatism, and Diabetes. (Zur Capillarresistenzbestimmung an der Bindehaut des Auges. Untersuchungsergebnisse an Gesunden, Kreislaufkranken, Hypertonikern, Rheumatikern, und Diabetikern.) HOFFMANN, R., and KRUGER, C. (1955). *v. Graefes Arch. Ophthal.*, **156**, 656. 6 refs.

Small haemorrhages which occur after applying for one minute suction of less than 300 mm. Hg on the bulbar conjunctiva and of less than 30 mm. Hg on the lower fornix must be considered as pathological. Only 70 per cent. of persons beyond the fiftieth year of life showed a normal capillary resistance. In the case of patients affected with disorders of the circulation or hyperpiesia this percentage is reduced to 60 per cent. It is astonishing that the capillary fragility was not found increased in diabetics. *H. Lytton.*

Researches on the Behaviour of the Serum C-Reactive Protein in Cases of Rheumatic Arthritis treated with Prednisone. (Ricerche sul comportamento della "proteina c reattiva" del siero in malati di artrite reumatoid curati con prednisone.) CARCASSI, V., and DANEO, V. (1956). *Reumatismo*, **8**, 19. 9 refs.

Serum Cholesterol Level in Acute and Chronic Arthritis. (Untersuchungen über den Cholesterinspiegel im Serum bei akuten und chronischen Arthritiden.) v. PLOTHO, B. (1955). *Klin. Med.* (*Wien*), **10**, 452.

Serum Diphenylamine Reaction in Chronic Rheumatic Diseases. (Die Diphenylaminreaktion im Serum bei chronisch-rheumatischen Erkrankungen.) GAMP, A. (1955). *Med. Klin.*, **50**, 2146. 17 refs.

Diphenylamine Reaction in Chronic Arthritis. (Die Diphenylaminreaktion bei chronischen Gelenkerkrankungen.) FÖRSTER, O., and SCHMID, J. (1955). *Z. Rheumaforsch.*, **14**, 364. 2 figs, 6 refs.

Determination of C-Reactive Protein as a Test for Rheumatic Fever. (La prueba de la determinación de la protéina reactica c en la fiebre reumática.). TRÍAS DE BES Y TERRÉS, J. (1956). *Med. clin.* (*Barcelona*), **14**, 19. 8 refs.

Behaviour of Antistreptolysin-O in Rheumatic Fever during Treatment with Cortisone in Small Doses. (Il comportamento delle antistreptolisine o nella malattia reumatica durante trattamento cortisonico a piccole dosi.) ROSSI, R. (1955). *Riv. Clin. pediat.*, **56**, 73. 1 fig.

Gel-Precipitation of Streptococcal Culture Supernates with Sera of Patients with Rheumatic Fever and Streptococcal Infection. HARRIS, T. N., HARRIS, S., and OGBURN, C. A. (1955). *Proc. Soc. exp. Biol.* (*N.Y.*), **90**, 39. 2 figs, 9 refs.

Changes in the Electrophoretic Protein Fractions of the Blood, in the Course of Acute Articular Rheumatism in Children. (Évolution des fractions électrophoretiques des protides sanguins au cours du rhumatisme articulaire aigu chez l'enfant.) FONTAN, A., VERGER, P., SZERSNOVICZ, G., MESNIER, F., and LODEON, J. (1956). *J. Méd. Bordeaux*, **133**, 127. 6 figs.

Liver Function Tests on Rheumatoid Arthritis Patients showing Complications associated with Gold Therapy. [In English.] LAINE, V., HOLOPAINEN, T., and KOSHINEN, H. M. (1955). *Acta rheum. scand.*, **1**, 196. 35 refs.

Arthrosis and Liver Function. (Artrosi e funzionalità epatica.) ANDREINI, A. (1955). *Reumatismo*, **7**, 363. Bibl.

Behaviour of Antistreptolysin-O in Rheumatic Diseases. (Sul comportamento della anti-streptolisine "O" nelle malattie reumatiche.) GIORDANA, M., FORTUNATO, A., and ARA, M. (1956). *Reumatismo*, **8**, 13. 2 figs, 15 refs.

Complement-Fixing Antigens in Concentrates of Streptococcal Culture Supernates. HARRIS, T. N. (1955). *Proc. Soc. exp. Biol.* (*N.Y.*), **90**, 33. 9 refs.

Study of the Waaler-Rose-Heller Reaction. (Etude de la réaction de Waaler-Rose-Heller.) GARRIC, P., PUTOIS, J., and RUFFIE, R. (1955). *Rev. Rhum.*, **22,** 678.

Soluble Collagens. [In English.] KULONEN, E. (1955). *Acta rheum. scand.*, **1,** 174. 4 refs.

Modification of the Niacin Furfuryl Reaction by Diphosphopyridin Nucleotide in Rheumatoid Arthritis. [In English.] HAYDU, G. G. (1955). *Acta rheum. scand.*, **1,** 177. 13 refs.

C-Reactive Blood Protein in Inflammatory Disease. Its Value as an Index of Rheumatic Activity. RUGGIERI, P. A. (1955). *J. med. Soc. N.J.*., **52,** 500.

ACTH, Cortisone, and Other Steroids.

Influence of ACTH and Cortisone on Certain Aspects of Aseptic Inflammation. [In Russian.] SMIRNOV, N. P. (1955). *Probl. Endokr. Gormonoter*, **1,** 81, No. 4. 1 fig., 3 refs.

The author reports that ACTH in doses of 2 units per kg. body weight twice daily retarded the appearance and hastened the absorption of inflammatory exudate in experimentally induced aseptic inflammation in the ears of rabbits; the inflammation was provoked by applying water at an initial temperature of 60° C. The volume of the ear was measured before, and again at 5 and 24 hours after the trauma, and thereafter daily for 7 days. In some of the experiments, the content of hyaluronidase in the exudate was determined by McClean's method, as modified by Smirnova. In control animals, the volume of the ear reached double its initial figure in 24 hours, then slowly diminished, but rarely returned to the initial volume within 7 days. In the majority of the animals treated with ACTH, the increase in size of the inflamed ears was less than double their initial volume (average 179·3 per cent.) and in all but two of fourteen animals they had returned to normal size within a week.

In another series of experiments, in which 5 units of ACTH per kg. body weight was administered on the 4th day after trauma, similar results were obtained; but if this dose of ACTH was given at the time of the injury, the period of exudation was prolonged, and the ear-volume at the end of 7 days was higher (119 per cent.) than in the control animals (113 per cent.). Finally, 5 units ACTH per kg. were given daily from the time of injury, together with 10 mg. cortisone per kg. from the fourth day. This addition of cortisone abolished the delay in reabsorption of exudates, and at the end of 7 days the volume of the ear was normal.

The explanation of these phenomena offered by the author is that repeated large doses of ACTH depress the function of the adrenal glands, thus actually suppressing the secretion of cortisone-like steroids. The effect of cortisone depends on the suppression or destruction of hyaluronidase, and consequent diminished permeability of the capillaries. The theory is supported by the results of estimations of hyaluronidase in the exudate from the ears of three groups each of twelve rabbits, of which one served as a control, one was given 5 units ACTH, and the third was given a preparation of ACTH which was inactive to biological tests. The content of hyaluronidase in 1 ml. exudate was 11·8, 6·5, and 9·3 per cent. in the three groups respectively, while the ear-volume at the same time, that is, 5 hours after injury, was 214·7, 159·2, and 198·3 per cent. of normal respectively.

[It is a pity that this last experiment was not extended to the animals receiving cortisone in addition to ACTH, and also to all groups at a somewhat later period of inflammation.]

L. Firman-Edwards.

Studies of 17-Hydroxycorticosteroids. IX. The Influence of Therapy on Adrenal Cortical Function in Patients with Rheumatic Fever. SEELY, J. R., ELY, R. S., DONE, A. K., AINGER, L. E., and KELLEY, V. C. (1955). *J. Pediat.*, **47,** 434. 1 fig., 18 refs.

The effect of prolonged hormone or salicylate therapy on adrenal cortical function was studied at the University of Utah, Salt Lake City, the response of the plasma 17-hydroxycorticosteroid concentration to injection of 25 units of ACTH being used as a test of this function. A total of 46 children, aged 6 to 15 years, with active rheumatic fever were divided into four groups according to the treatment given, as follows:

(1) salicylates (six patients);
(2) cortisone by mouth (fourteen);
(3) lyophilized ACTH (eighteen);
(4) ACTH gel (eight).

The duration of treatment ranged from 22 to 106 days (mean 47 days) and the maximum daily doses were approximately 1 unit ACTH per lb. (2·2 units per kg.), 2 to 3 mg. cortisone per lb. (4·4 to 6·6 mg. per kg.), and 60 mg. salicylate per lb. (132 mg. per kg.) body weight.

In all groups, except the group given ACTH gel, the mean plasma 17-hydroxycorticosteroid level was significantly lower during the post-treatment period (within 10 days of stopping the drug) than during the pre-treatment period, but not significantly lower than in untreated patients with active rheumatic fever of the same duration. In all groups the response of the 17-hydroxycorticosteroid level to intramuscular injection of ACTH was normal during the pre-therapy period; during the post-treatment period the magnitude of this response was reduced significantly in the cortisone- and the salicylate-treated groups but not in the ACTH-treated groups. In cortisone-treated patients the ACTH-response test was applied at varying times after treatment ceased. The results indicated that depression of steroid response persists for no longer than one week after discontinuation of cortisone. No relationship was observed between duration of cortisone therapy or daily dose of the drug and the magnitude of the ACTH steroid response. [No explanation is offered for the decreased adrenal responsiveness in the post-treatment period in patients given salicylates.] *C. E. Quin.*

Physical Effects of ACTH and Cortisone in Children. (Effets psychiques de l'ACTH et de la cortisone chez l'enfant.) MOZZICONACCI, P., KOUPERNIK, C., and LYARD. (1955). *Bull. Soc. méd. Hôp. Paris*, **71**, 531.

In a study of 57 children under treatment with cortisone at the Clinique Médicale des Enfants, Paris, for various illnesses side-effects attributable to the drug were observed in 46. In all but two of these cases the reactions were minor, consisting of morbidly increased appetite, sleeplessness, restlessness occasionally amounting almost to hypomania, and states of temporary anxiety and depression. The two severe upsets occurred in a 7-year-old boy who developed a hallucinated confusional state and a 5-year-old girl who went into convulsions and coma from which she emerged in a state of idiocy. [The role of cortisone in the aetiology of this second case is speculative.]

The authors emphasize that reactions are most prone to occur at the beginning and end of treatment. Most of the patients showing reactions also showed signs of hypercorticism, and this may be an indicator of susceptibility. An abnormal electroencephalogram did not seem to be a pointer, but a neuropathic family history was often elicited. The authors do not consider that minor manifestations need be a contraindication to use of cortisone when this is necessary, but suggest that in such cases the dose should be reduced or treatment given intermittently. *M. E. MacGregor.*

Use of "Metacortandracin" [Prednisone] and 9-α-Fluoro Hydrocortisone Acetate in the Rheumatic Diseases. (L'impiego del metacortandracin e del 9-α-fluoro idrocortisone acetato nelle malattie reumatiche.) BALLABIO, C. B., AMIRA, A., CIRLA, E., and SALA, G. (1955). *Reumatismo*, **7**, 113. 9 figs, 5 refs.

At the Centre of Rheumatology of the University of Milan fourteen patients (nine males and five females ranging in age from 7 to 71) suffering from rheumatoid arthritis (seven cases) or other rheumatic disorders were treated with prednisone ("metacortandracin") or 9-α-fluoro hydrocortisone. Most of them had previously been treated with cortisone or hydrocortisone, ACTH, or phenylbutazone. Both drugs were given by mouth, the initial dose being 30 to 50 mg. for prednisone and 8 to 16 mg. for 9-α-fluoro hydrocortisone. The duration of treatment varied according to experimental requirements, but in some cases the same scheme of treatment was used as cortisone.

Both steroids showed a definite anti-rheumatic effect, prednisone proving three to four times more effective than cortisone and 9-α-fluoro hydrocortisone eight to ten times more active. Salt and water metabolism was not influenced by prednisone but was much disturbed by 9-α-fluoro hydrocortisone, which caused oedema with salt and water retention. For that reason the latter was regarded as unsuitable for clinical use. Both steroids produced signs of hyperadrenalism, varying in degree with the dosage and length of treatment and similar to those caused by cortisone and hydrocortisone. The authors stress the practical importance of the absence of any effect of prednisone on fluid balance, making it suitable even for patients with a failing heart. *V. C. Medvei.*

Treatment of Bronchial Asthma with Corticotrophin (ACTH). [In Russian.] KOGAN, B. B. (1955). *Klin. Med.* (*Mosk.*), **33**, 49. 1 ref.

The author begins by pointing out that ACTH (corticotrophin) is not a specific remedy for asthma or its allergic component, but only produces a remission of varying duration. The hormone acts by stimulating the function of the adrenal cortex and has also a spasmolytic action.

In clinical use for the treatment of bronchial asthma the author found that, providing there were no contraindications such as tuberculosis, hypertension, marked arteriosclerosis, or ulcerative disease, the administration of small or moderate doses of the hormone (20 to 40 units in 24 hours) caused no notable side-effects within 2 to 3 weeks. Palpitations, tachycardia, restlessness, insomnia, and headache were observed in only two out of a large number of patients.

The author states that the most striking advantage of ACTH over other spasmolytic agents such as adrenaline or ephedrine is the favourable action which it exerts on the patient's general health. The hormone is very useful in treating status asthmaticus or in cases in which repeated injections of adrenaline are contraindicated. *H. W. Swann.*

Mechanism of Action of Intra-Articular Hydrocortisone. (Le mécanisme d'action de l'hydrocortisone injectée dans les articulations.) COSTE, F., ANTOINE, B., and RAMPON, S. (1955). *Rev. Rhum.*, **22**, 657. 14 refs.

The greater efficacy of hydrocortisone acetate over the cortisone ester when given by intra-articular injection is usually attributed to its relative insolubility. The authors have carried out a trial with a more soluble ester of hydrocortisone (the hemisuccinate), comparing the effect of this in solution with that of the usual acetate suspension, either in homologous joints or, alternately, in succession into the same joints; 27 injections of each were given to seven male patients.

It was found that the hemisuccinate was slightly more effective than the acetate (although it caused some pain on injection); 5 mg. hemisuccinate was given in six cases, and was nearly as effective as 25 mg. acetate into the same joints. It would appear, therefore, that the greater efficacy of hydrocortisone over cortisone is not due to the insolubility of the ester normally used. After discussing all the evidence the authors conclude that hydrocortisone is probably more effective because it can exert an immediate action on tissue, without any preliminary metabolic process. *B. E. W. Mace.*

ERRATUM

It is regretted that in the article by Millard and Barber, *Annals of the Rheumatic Diseases* (1956), **15**, 53, Table II, the results in Section 2 C Intravenous, and Section 2 D Intramuscular have been transposed. The Table should read correctly as follows:

TABLE II

ERYTHROCYTE SEDIMENTATION RATES
(mm./hr. Westergren)

Group	Series	Time since Admission (wks)	0	2	6	10	14
(1)	A Oral	0–19	1	0	1	1	0
		20–39	1	4	1	2	2
		40–59	2	4	8	7	2
		60–79	1	5	3	4	2
		80–99	7	9	8	3	2
		100 and over	1	3	4	3	2
		Total	13	25	25	20	10
		Average	71	71	70	65	69
	B Intravenous	0–19	0	0	1	1	0
		20–39	3	5	6	4	2
		40–59	5	5	6	7	6
		60–79	0	4	3	3	1
		80–99	2	2	2	1	2
		100 and over	3	5	3	1	0
		Total	13	21	21	17	11
		Average	62	66	55	49	53
(2)	C Intravenous	0–19	0	0	1	0	0
		20–39	3	5	7	5	2
		40–59	6	3	6	4	2
		60–79	1	6	1	3	2
		80–99	7	4	5	2	2
		100 and over	5	4	2	4	2
		Total	22	22	22	18	10
		Average	72	66	55	63	70
	D Intramuscular	0–19	0	0	2	3	0
		20–39	4	6	7	5	2
		40–59	8	7	3	6	8
		60–79	6	6	10	4	1
		80–99	5	5	2	3	1
		100 and over	1	1	1	1	0
		Total	24	25	25	22	12
		Average	60	62	51	49	49

Ann. rheum. Dis. (1956), **15**, 211.

RHEUMATOID ARTHRITIS AND THE POSITIVE L.E.-CELL PHENOMENON

BY

J. H. KIEVITS, J. GOSLINGS, H. R. E. SCHUIT, AND W. HIJMANS

Department of Rheumatology, University Hospital, Leiden, Netherlands

(RECEIVED FOR PUBLICATION APRIL 23, 1956)

Kaposi (1872) first drew attention to the fact that joint symptoms occur in a great number of cases of systemic lupus erythematosus. Reifenstein, Reifenstein, and Reifenstein (1939) compiled data from eighteen patients and noted articular manifestations in all. Klemperer, Pollack, and Baehr (1941) noticed that in ten out of twenty of their patients joint symptoms were the first manifestations of the disease. In a more recent study, Dubois (1953) mentions that 90 per cent. of a series of 62 patients had joint involvement, ranging from ill-defined arthralgia to joint deformities with bone destruction similar to those seen in rheumatoid arthritis. In this same series, 30 per cent. had "definite rheumatoid deformity". In a group of 105 cases, analysed by Harvey, Shulman, Tumulty, Conley, and Schoenrich (1955), only ten had no joint involvement, and in 63 per cent. the articular manifestations occurred during the initial episode of the illness; the arthritis was described as typical of rheumatoid arthritis in 28 of these patients.

It is now generally accepted that Hargraves's L.E.-cell test (Hargraves, Richmond, and Morton, 1948) is a useful diagnostic method for detecting systemic lupus erythematosus, especially since this test can be positive in an early stage of the disease and also in the mono- or oligosymptomatic phase. If this test could be considered to be absolutely specific, it would then seem possible to diagnose some cases of rheumatoid arthritis as mono- or oligosymptomatic forms of systemic lupus erythematosus.

To investigate this possibility two series of adult patients with rheumatoid arthritis were studied, and the L.E.-cell phenomenon was found to be positive in 17 and 15 per cent. respectively. Statistical analysis of certain signs and symptoms in the patients with and without a positive L.E. phenomenon showed significant differences.

Material and Methods

Only adults suffering from straightforward rheumatoid arthritis of the peripheral joints, diagnosed on generally accepted clinical criteria, were included. Those whose history and clinical findings were of a dubious nature were excluded, as were also patients with ankylosing spondylitis. The Zimmer and Hargraves (1952) blood-clot technique was used in making L.E.-cell preparations, with the addition of an interval of 10 to 20 minutes between fragmentation of the blood clot and centrifugation. From every patient four preparations were made and stained by the Giemsa method. Each preparation was examined microscopically with a 10× eyepiece and a 25× objective lens for at least 15 minutes. All suspected cells were then further examined by oil-immersion magnification. According to the criteria of Hargraves and others (1948), the phagocytosed inclusion bodies were distinguished from other phagocytic phenomena, especially nucleo-phagocytosis. For the purpose of this study a preparation was called positive if one or more L.E. cells or rosettes were seen.

Series A consisted of 388 cases of rheumatoid arthritis, which however did not include all patients available during that period. In order to exclude the unintentional selection of possible cases of lupus erythematosus, Series B comprised one hundred unselected consecutive cases of rheumatoid arthritis as they were admitted to our department. In Series C (controls) the Hargraves test was applied in 54 cases of active tuberculosis, fourteen cases of chronic nephritis, and thirteen cases of active discoid forms of lupus erythematosus. The test was also applied to 444 cases from the Department of

TABLE I

MATERIAL STUDIED

Series	Diagnosis	No. of Patients	Positive L.E. Test	
			No.	Per cent.
A	Rheumatoid Arthritis	388 } 488	66 } 81	17 } 17
B	Rheumatoid Arthritis	100 }	15 }	15 }
C	Tuberculosis	54 } 81	0	
	Nephritis	14 }	0	
	Discoid Lupus Erythematosus	13 }	0	
D	Other Unspecified Diseases	444†	19‡	
E	Other Rheumatic Diseases:			
	Arthralgias	70 } 119	1*	
	Ankylosing Spondylitis with Peripheral Arthritis	11 }	1	
	Ankylosing Spondylitis without Peripheral Arthritis	8 }	0	
	Osteo-Arthritis	23 }	0	
	Peri-Arthritis	7 }	0	

* Who later developed rheumatoid nodules.
‡ Eighteen systemic lupus erythematosus and one scleroderma.
† Sent to our department by the Department of Medicine.

Medicine in which the diagnosis was unknown to us (Series D). Furthermore, 119 additional cases of rheumatic disease other than rheumatoid arthritis were studied (Series E).

Various signs and symptoms were analysed statistically in fifty unselected cases of rheumatoid arthritis with positive L.E. phenomenon (LE+) and a hundred consecutive cases of rheumatoid arthritis without positive L.E. phenomenon (LE−).

With the exception of information regarding lower respiratory tract infection, and that regarding erythrocyte sedimentation rate after gold therapy, the data were obtained at the time of the L.E.-cell examination.

Results

The results of the L.E.-cell examinations are given in Table I. This test was positive in 17 per cent. of the group of 388 cases of rheumatoid arthritis (Series A) and in 15 per cent. of the consecutive series of 100 cases (Series B).

No L.E. cells were seen in the control group of 81 patients, comprising 54 cases of active tuberculosis, fourteen cases of chronic nephritis, and thirteen cases of active discoid lupus erythematosus (Series C).

In the slides of 444 other cases sent to our laboratory by the Department of Medicine, L.E. cells were found in nineteen instances (Series D). In eighteen of these cases, the clinical diagnosis was systemic lupus erythematosus or the findings were compatible with this diagnosis. In one case the patient was suffering from scleroderma.

In 119 cases with a diagnosis of a rheumatic disease other than rheumatoid arthritis (Series E) L.E. cells were found twice: in one of these, a patient with unclassified arthralgia, rheumatoid nodules developed 3 weeks after the test was done, and the other patient was suffering from ankylosing spondylitis with peripheral arthritis. Both cases therefore showed signs and symptoms compatible with the syndrome of rheumatoid arthritis.

Table II (opposite) indicates which of the signs and symptoms used in comparing the fifty cases of LE+ with the one hundred consecutive cases of LE− showed significant differences.

No differences were found in sex distribution or duration of illness (Table III, opposite).

The results in Table IV (opposite) were analysed by the exact method of Fisher (1954) using the χ^2 test.

Splenomegaly (Table IV) occurred six times in the LE+ group and only once in the LE− group. On the basis of $P=0{\cdot}006$, the difference is statistically significant.

Diseases of the Lower Respiratory Tract (Table IV) were found in fourteen patients, either on clinical or roentgenological examination or in the previous history; nine cases belonged to the LE+ group and five to the LE− group. The difference is statistically significant ($P=0{\cdot}02$), but this did not apply when only the chest *x* rays made at the same time as the L.E.-cell test, were analysed.

Urinary Sediment (Table IV—excluding cases of bacterial origin) occurred with greater frequency in the LE+ group ($P=0{\cdot}006$). This was not the case with albuminuria.

TABLE II

CLINICAL SIGNS AND SYMPTOMS IN FIFTY CASES OF LE+ COMPARED WITH THOSE IN ONE HUNDRED CONSECUTIVE CASES OF LE−

Signs		Statistically Significant Difference
General	Sex distribution	No
	Duration of illness	No
	Age	No
	Fever	No
	Loss of weight	No
Skin	Erythematous group	No
	Rheumatic nodules	No
Visceral Organs	Lungs (*x* ray)	No
	Diseases of respiratory tract (pneumonia, purulent bronchitis, pleuritis)	Yes
	Cardiac murmurs	No
	Electrocardiographic changes	No
	Blood pressure	No
	Adenopathy	No
	Hepatomegaly	No
	Splenomegaly	Yes
	Renal lesions: albuminuria, abnormal urinary sediment	No Yes
Haematology	Haemoglobin (Table IV)	Yes
	White blood count	No
	Erythrocyte sedimentation rate (Table V)	Yes
Serology	Wassermann reaction (Table IV)	Yes
	Antistreptolysin titre	No
	Sheep-cell agglutination	No
Joint Pathology	Initial stage (acute or non-acute)	No
	Initial localization (small or large joints)	No
	Severity of bone destruction	No
Therapy	Effect of first course of gold on sedimentation rate (Table V)	Yes
	Intoxication reactions during first course of gold	No

False-Positive Test for Syphilis (Table IV).—A positive Wassermann reaction was found with greater frequency in the LE+ group, but, as our attention was drawn to this reaction in a late stage of the study, the number of unknowns is high. On the basis of the known figures, the difference is statistically significant ($P=0{\cdot}002$). The Meinicke reaction was negative in six out of the eight cases with a positive Wassermann reaction. It is reasonable to assume that all positive tests were so-called false-positive, as none of these patients had a luetic infection as judged by other routine criteria.

TABLE III

SEX DISTRIBUTION AND DURATION OF ILLNESS

L.E. Cells		+	−	Total
Duration (yrs)	<1	4	16	20
	1–2	7	13	20
	2–3	7	7	14
	3–5	6	11	17
	5–10	13	21	34
	10–20	8	24	32
	>20	5	7	12
	Unknown		1	1
	Total	50	100	150
Sex	Male	15	41	56
	Female	35	59	94
	Total	50	100	150

TABLE IV

NUMERICAL ANALYSIS OF DIFFERENCES FROM TABLE II WHICH ARE STATISTICALLY SIGNIFICANT BY THE χ^2 TEST

L.E. Cells		+	−	Total
Spleen	Palpable	6	1	7
	Not palpable	44	98	142
	Total	50	99	149
	$P=0{\cdot}006$ Unknown	0	1	1
	Total	50	100	150
Diseases of Lower Respiratory Tract	Present	9	5	14
	Absent	38	93	131
	Total	47	98	145
	$P=0{\cdot}02$ Unknown	3	2	5
	Total	50	100	150
Urinary Sediment	Abnormal	8	3	11
	Normal	38	91	129
	Total	46	94	140
	$P=0{\cdot}006$ Unknown	4	6	10
	Total	50	100	150
Wassermann Reaction	Positive	8	0	8*
	Negative	27	42	69
	Total	35	42	77
	$P=0{\cdot}002$ Unknown	15	58	73
	Total	50	100	150
Erythrocyte Sedimentation Rate after Gold Therapy	Reduced to Normal	2	25	27
	Not reduced	15	13	28
	Total	17	38	55
	$P=0{\cdot}0002$ Unsatisfactory reduction	8	16	24
	Unknown	25	46	71
	Total	50	100	150

* Wass. R. + / Mein. R. + : 2 — Wass. R. + / Mein. R. − : 6

The results in Table V are calculated by the method of Smirnov (1948).

Haemoglobin (Table V).—The first LE+ column gives the cumulative numbers and the next column the cumulative percentages of regularly increasing haemoglobin values. The haemoglobin level of the LE+ patients is lower than that in the LE− group. The difference is statistically highly significant ($P=0\cdot0004$).

Erythrocyte Sedimentation Rate (Table V).—This was measured on the same day as the L.E.-cell examination. It is given in cumulative numbers and percentages. The difference is statistically significant ($P=0\cdot03$). L.E. cells were found in five patients whose sedimentation rates were lower than 10 mm. in the first hour (Westergren).

TABLE V

CUMULATIVE DISTRIBUTION OF HAEMOGLOBIN AND ERYTHROCYTE SEDIMENTATION RATE

L.E. Cells		+		−	
		Cases	Per cent.	Cases	Per cent.
Percentage Haemoglobin (g.)	<46 (7·4)				
	<51 (8·2)	3	6·2		
	<56 (9·0)	8	16·7		
	<61 (9·8)	11	22·9	6	6·8
	<66 (10·6)	15	31·2	15	17·0
	<71 (11·4)	32	66·7	26	29·5
	<76 (12·2)	37	77·1	39	44·3
	<81 (13·0)	40	83·3	63	71·6
	<86 (13·8)	44	91·7	78	88·6
	<91 (14·6)	44	91·7	85	96·6
	<96 (15·4)	47	97·9	87	98·0
	<101 (16·2)	48	100·0	88	100·0
	D. max.=66·7−29·5=37·2 per cent. (Smirnov test) $P=0\cdot0004$				
	Unknown	2		12	
	Total ..	50		100	
Erythrocyte Sedimentation Rate (Westergren mm./hr.)	>100 ..	4	8·0	2	2·0
	> 80 ..	12	24·0	9	9·3
	> 60 ..	21	42·0	16	16·5
	> 50 ..	24	48·0	22	22·7
	> 40 ..	29	58·0	35	36·0
	> 30 ..	36	72·0	56	57·7
	> 20 ..	42	84·0	72	74·2
	> 10 ..	45	90·0	83	85·5
	> 0 ..	50	100·0	97	100·0
	D. max.=42·0−16·5=25·5 per cent. (Smirnov test) $P=0\cdot03$				
	Unknown	0		3	
	Total ..	50		100	

A reduction in sedimentation rate after a first course of gold therapy (Table IV), occurred in 25 out of 38 cases in the LE− group and in only two out of seventeen cases in the LE+ group. ($P=0\cdot0002$.) Unfortunately, the number of unknowns is high, and this result cannot therefore be applied to the whole group.

The occurrence of L.E. cells in rheumatoid arthritis can therefore be more or less confidently expected, but it is not possible to relate the findings of L.E. cells to a typical clinical picture.

Discussion

The majority of papers dealing with the specificity of the L.E.-cell test have been discussed in the monograph by Harvey and others (1955). This test seems to be highly specific for systemic lupus erythematosus, but is also positive in a certain percentage of cases of penicillin-hypersensitivity and in some patients treated with hydralazine. In addition L.E. cells have been found in individual patients suffering from a variety of diseases. In many of these, however, it is reasonable to assume from the descriptions that the cells in question were not true L.E. cells, but other inclusion bodies, more or less resembling those originally described by Hargraves. It is essential to adhere to his criteria and to exclude the presence of tartcells, erythrophagocytosis, or other phenomena, such as those described by Lee, Michael, and Vural (1951) and Inderbitzin (1953). Some of these can be distinguished with special staining techniques, as they do not contain nuclear substances. In nine of our cases an extended Feulgen technique (Duijn, 1956) was applied; they were all positive, suggesting the presence of nuclear material.

In this study, L.E. cells were found in 17 per cent. of 488 cases of rheumatoid arthritis. Because of the reproducibility, histochemical investigations, and negative results in control series, laboratory error can safely be excluded.

Three possible explanations of the diagnostic significance of this frequent occurrence of L.E. cells in rheumatoid arthritis are discussed below:

(1) *The test is not specific.*—This seems unlikely as a control series yielded negative results: no L.E. cells were seen in the slides of the cases listed in Table I, comprising 54 patients suffering from active tuberculosis, fourteen with chronic nephritis, and thirteen with discoid lupus erythematosus. Of 444 cases suffering from various disorders, L.E. cells were found in nineteen: in eighteen of these the diagnosis of systemic lupus erythematosus was compatible with the clinical picture. One patient was suffering from scleroderma; Volpé and Hauch (1955) also found L.E. cells in this disease.

Only two out of 119 patients, who were suffering from rheumatic disease but in whom the diagnosis of rheumatoid arthritis was not made when the L.E. test was done, had positive slides. In one, rheumatic nodules appeared 3 weeks later, and the other was suffering from ankylosing spondylitis with peripheral arthritis. Therefore rheumatoid arthritis occupies a unique place in this assumed non-specificity of the L.E.-cell phenomenon.

(2) *The test is specific.*—Every case with L.E. cells could then be diagnosed as suffering from systemic

lupus erythematosus. This is a simple but not very satisfactory solution, as it seems hardly justified to classify a syndrome with unknown aetiology and unknown pathogenesis on the basis of an unexplained laboratory phenomenon. The following case-history illustrates the difficulty of accepting this theory for clinical reasons:

A 36-year-old woman visited the out-patient department for the first time in 1935 because of a migrating poly-arthritis with tenderness and swelling, involving the shoulders, elbows, wrists, hands, and knees. On further examination a chronic tonsillitis was found, but tonsillectomy was refused. The erythrocyte sedimentation rate was slightly increased (16 and 19 mm. in the first hour). Analgesics were prescribed and her condition remained fairly satisfactory for the next 10 years. From 1945 onwards the poly-arthritis deteriorated gradually and 1948 rheumatoid arthritis was diagnosed on the basis of clinical and *x*-ray findings. She greatly improved after tonsillectomy.

In June, 1953, she was seen by Dr. Fontein, to whom we are indebted for the following information:

For one year the arthritis has been progressive and the patient has complained of severe dizziness. She presented the typical picture of active rheumatoid arthritis with a flexion contracture of the left knee. A soft systolic murmur was heard over the apex and over the left border of the sternum. The dizziness remained unclassified. Laboratory data:

Erythrocyte sedimentation rate 39 mm./hr.
Hb. 63 per cent.
Normal white blood count of 6,100 cells per c.mm. and a slight thrombopenia with 140,000 platelets.

A month later the patient developed a venous thrombosis of the left leg. As this was thought to be exceptional in rheumatoid arthritis, L.E.-cell preparations were made, which were repeatedly and strongly positive. In October, 1953, the patient was discharged in a greatly improved condition, the erythrocyte sedimentation rate being 12 mm./hr. The improvement was maintained when she was seen in April, 1954; the heart murmurs were unchanged and could not in themselves be taken to indicate a structural change. Soon afterwards she again became bedridden. On physical examination in April, 1956, the arthritis was not very active and no murmurs were heard. The L.E.-cell phenomenon was still positive.

If in such a case, with a 20 year's history of typical, clinical rheumatoid arthritis, the diagnosis has to be changed to systemic lupus erythematosus on the basis of L.E. cells after the occurrence of a thrombosis, every patient with the syndrome of rheumatoid arthritis should be suspected as a possible case of disseminated lupus erythematosus. This diagnosis does not indicate a disease entity, but only another clinical syndrome with unknown aetiology and pathogenesis.

(3) *The results of the test are to be treated as purely descriptive.*—About 17 per cent. of patients with rheumatoid arthritis show L.E. cells in preparations from peripheral blood. As a group they differ in certain respects from other cases of rheumatoid arthritis without L.E. cells. This difference concerns the spleen, the lower respiratory tract, the haemoglobin level, the urinary sedimentation, possibly the Wassermann reaction, the erythrocyte sedimentation rate, and the reaction to gold therapy.

At the present stage of our knowledge, this approach seems preferable to the other two; it is the least dogmatic and the most flexible, and by not giving a definite answer should stimulate further investigations.

It has been reported (Ishmael, 1955; Slocumb, 1955) that cortisone therapy increases the frequency of L.E. cells in rheumatoid arthritis. In our series there were only two among the 100 patients of the LE− group, who had received ACTH before the L.E.-cell examination. Of the fifty patients of the LE+ group, there were seven who had been treated with either ACTH or cortisone, but in three of them L.E. cells had been found before the institution of hormone therapy. As no L.E.-cell preparations were made in the remaining four patients before treatment, it is not possible to evaluate the influence of hormone administration on the L.E. phenomenon. This reported increased frequency of L.E. cells in rheumatoid arthritis after cortisone treatment might be due to the fact that these patients were selected for treatment for the same reasons which classify them in our LE+ group: a low haemoglobin value, a greatly increased erythrocyte sedimentation rate, or an unsatisfactory reaction to gold therapy.

Summary

L.E. cells were found in 17 per cent. of 488 cases of rheumatoid arthritis. This observation led to a statistical analysis of its clinical implications. The group with positive L.E.-cell phenomenon showed a higher frequency of splenomegaly, diseases of the lower respiratory tract, abnormal urinary sediment, anaemia, false positive tests for syphilis and a high erythrocyte sedimentation rate which failed to fall after a first course of gold treatment.

In individual cases of rheumatoid arthritis the positive L.E.-cell phenomenon was not related to a typical clinical picture.

We should like to acknowledge the support received from Prof. Dr. J. Mulder (Department of Medicine) and Prof. Dr. A. Querido (Department of Endocrinology and Metabolic Diseases) and their staffs; we are indebted to Dr. E. H. J. Warns and the staff of the Rotterdamsch Zeehospitium for the blood samples of patients with tuberculosis and to Dr. E. F. Drion (Statistics Department, T.N.O.) for statistical advice.

REFERENCES

Dubois, E. L. (1953). *Ann. intern. Med.*, **38**, 1265.
Duijn, P. van (1956). *J. Histochem. Cytochem.*, **4**, 55.
Fisher, R. A. (1954). "Statistical Methods for Research Workers" 12th ed., p. 96. Oliver and Boyd, Edinburgh.
Hargraves, M. M., Richmond, H., and Morton, R. (1948). *Proc. Mayo Clin.*, **23**, 25.
Harvey, A. McG., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. (1955). "Systemic Lupus Erythematosus". Williams and Wilkins, Baltimore. (*Medicine (Baltimore)*, (1954), **33**, 291).
Inderbitzin, T. (1953). *J. invest. Derm.*, **20**, 67.

Ishmael, W. K. (1955). *Discussion of* McCoy, Patterson, and Freyberg (1955).
Kaposi, M. K. (1872). *Arch. Derm. Syph. (Prag.)*, **4**, 36.
Klemperer, P., Pollack, A. D., and Baehr, G. (1941). *Arch. Path. (Chicago)*, **32**, 569.
McCoy, F. W., Patterson, M., and Freyberg, R. H. (1955). *Annals of the Rheumatic Diseases*, **14**, 415.
Lee, S. L., Michael, S. R., and Vural, I. L. (1951). *Amer. J. Med.*, **10**, 446.
Reifenstein, E. C., Reifenstein, E. C., Jr., and Reifenstein, G. H. (1939). *Arch. intern. Med.*, **63**, 553.
Slocumb, C. H. (1955). *Discussion of* McCoy, Patterson, and Freyberg (1955).
Smirnov, N. (1948). *Ann. math. Statist.*, **19**, 279.
Volpé, R., and Hauch, J. T. (1955). *Can. med. Ass. J.*, **72**, 597.
Zimmer, F. E., and Hargraves, M. M. (1952). *Proc. Mayo Clin.*, **27**, 424.

L'arthrite rhumatismale et le phénomène positif des cellules du lupus érythémateux

RÉSUMÉ

Des cellules L.E. furent décelées dans 17 pour cent de 488 cas d'arthrite rhumatismale. Cette observation conduisit à une analyse statistique de ses implications cliniques. Le groupe au phénomène des cellules L.E. positif accusa une plus grande fréquence de splénomégalie, de maladies des voies respiratoires inférieures, de sédimentation urinaire anormale, d'anémie, de fausses réactions positives pour la syphilis, ainsi qu'une vitesse de sédimentation globulaire élevée qui ne diminua pas après la première étape du traitement aux sels d'or.

Dans des cas individuels d'arthrite rhumatismale, le phénomène positif des cellules L.E. ne se rapportait à aucun tableau clinique typique.

La artritis reumatoide y el fenómeno positivo de células del lupus eritematoso

SUMARIO

Células L.E. fueron encontradas en el 17 por ciento de 488 casos de artritis reumatoide. Esta observación llevó a una análisis estadística de sus implicaciones clínicas. El grupo con el fenómeno de células L.E. positivo manifestó mayor frecuencia de esplenomegalia, de enfermedades de las vías respiratorias inferiores, de sedimentación urinaria anormal, de anemia, de falsas reacciones sifilíticas así como una velocidad de sedimentación eritrocitaria alta que no bajó después de la primera serie de crisoterapia.

En casos individuales de artritis reumatoide, el fenómeno positivo de células del lupus eritematoso no se relacionaba con ningún cuadro clínico típico.

Ann. rheum. Dis. (1956), **15**, 217.

NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

III. CHANGES IN THE BONE MARROW AND THEIR RELATION TO OTHER FEATURES OF THE DISEASE

BY

J. RICHMOND, D. L. GARDNER, L. M. H. ROY, AND J. J. R. DUTHIE

From the Rheumatic Unit, Northern General Hospital, Edinburgh

(RECEIVED FOR PUBLICATION MAY 10, 1956)

In a previous report (Roy, Alexander, and Duthie, 1955), the characteristics of the anaemia in rheumatoid arthritis were reviewed and it was shown that, although hypochromia of the red cell was a consistent feature, absorption of iron from the gut was unimpaired. On the other hand, the level of iron in the plasma was subnormal in the majority of cases and iron in the form of saccharated oxide, when administered by the intravenous route, was removed from the plasma of patients with rheumatoid arthritis more rapidly than from that of normal individuals. It had already been shown by Sinclair and Duthie (1949, 1950) and by others (Ross, 1950; Jeffrey, 1952, 1953a, 1953b) that improvement in the anaemia followed the therapeutic use of intravenous iron in a proportion of cases of rheumatoid arthritis, although there was no relationship between the abnormality of iron metabolism, the degree of anaemia, and the response to treatment.

In these circumstances it was felt that a detailed study of the bone marrow with particular reference to the presence or absence of iron would be of considerable importance. The principal object of the investigation was to estimate the iron content of the marrow in a series of patients suffering from rheumatoid arthritis in order to determine whether the quantity of iron in the marrow was related to the degree of anaemia, the plasma iron level, the activity of the disease, or its duration. In addition, it was decided to study the cytology of the marrow in detail in order to define any characteristic or consistent changes in the cell pattern and to relate these changes to other features of the disease.

Review of Literature

Iron Content of Marrow.—In recent years it has been shown that iron may be demonstrated in marrow obtained at biopsy using an appropriate staining technique. Rath and Finch (1948) described the value of this procedure and claimed that the absence of stainable iron from the marrow indicated the need for the administration of iron. They examined 63 cases with a variety of diseases and found that anaemia due to deficiency of iron was associated with absence of stainable iron from the marrow. In anaemia due to infection and in pernicious anaemia, the iron content of the marrow tended to be high. Eleven of their cases were said to be normal and the marrows contained iron in small to moderate amounts. In their experience, only those cases in whom stainable iron was absent from the marrow responded to iron therapy. Masshof and Gruner (1951) found that the amount of iron which could be identified in the marrow by histochemical methods bore no relationship to the nature of the anaemia. Davidson and Jennison (1952) estimated the stainable iron content in 165 marrow samples from individual patients with a variety of diseases. The serum iron concentration was measured in 72 cases. Small to moderate amounts of iron were seen in the marrow from eleven patients without anaemia. They found that in iron deficiency anaemia there was no stainable iron in the marrow and the serum iron levels were low. In pernicious anaemia the iron content of the marrow was high and the serum iron level high. In the anaemia of sepsis and uraemia the amount of stainable iron in the marrow was high, but the level of serum iron low. The largest amounts of iron found in the marrow were in cases following repeated blood transfusion. Hutchison (1953), in a series of 141 cases, confirmed the findings of Rath and Finch (1948). He also claimed that, if iron was present in the marrow, the anaemia would not respond to iron administered orally or by the intravenous route. There were seventeen normal individuals in this group and iron was present in the marrow of all these subjects in amounts which could be easily recognized. Stevens, Coleman, and

Finch (1953) agreed that stainable iron was absent from the marrow in anaemia due to iron deficiency and that there was a tendency for the iron content to be high in anaemia which was not associated with blood loss. In their series of 298 cases, there were 31 with normal blood findings. In four of these cases stainable iron was absent or present only in small amounts.

There are few accounts of the iron content of the bone marrow in rheumatoid disease. Smith (1953) estimated the iron in three cases of rheumatoid arthritis. Stainable iron was present in two cases and absent in the remaining case. She also studied the marrow of twenty normal individuals and failed to find stainable iron in four. Pratt and Johnson (1954) studied 116 patients suffering from a variety of diseases. There were five cases of rheumatoid arthritis in their series and they claimed that the iron content of the marrow was greater than normal in four.

Cytology of Marrow.—The cytology of the marrow in rheumatoid arthritis has been studied by several authors and the account given by Mester (1938) is among the earliest available. He described 33 cases of "primary chronic joint rheumatism" and claimed that an increase in plasma cells paralleled the activity of the disease. Kaether (1938) investigated 26 cases and regarded toxic granulation of the neutrophil polymorphs as characteristic of rheumatoid disease. Michelazzi (1937) reported a single case; he found proliferation of reticulo-endothelial and plasma cells. Marrow from 55 cases of "chronic polyarthritis" was examined by Fleischhacker and Lachnit (1940). They stated that a significant increase in reticulum cells and a slight plasmacytosis commonly occurred; only one case was described in detail and it was not stated how many of their cases were suffering from rheumatoid arthritis. Merlo and Tortori-Donati (1945) described "histiolymphocytosis" in each of seven cases; in three the myeloid-erythroid ratio was less than 2:1. Luchesi, Luchesi, and Da Silva (1946) discussed 32 cases; they gave few details but claimed that plasmacytosis was typical. Marmont (1948), in an exhaustive review of 21 cases, found "active reticulo-endothelial systems", eosinophilia, plasmacytosis, and a tendency to megaloblastosis. Nilsson (1948) described only the erythroid series; on the basis of the twelve marrows examined, he claimed that a delay in the maturation of red cells was common. Leitner (1949) gave details of two cases and concurred with the findings of Mester (1938). In a widely-quoted paper, Hayhoe and Smith (1951) described the marrow in ten cases of rheumatoid disease. They found that the plasma cells exceeded 2 per cent. in nine cases, and in six where the plasma proteins had been estimated hyperglobulinaemia was recorded and associated with plasmacytosis in each instance. Jasiński and Staehelin (1951), however, made a detailed study of 20 cases and found plasmacytosis in only three instances. Finch, Crockett, Ross, and Bayles (1951) claimed that there was moderate depression of the red cell series but gave few details. Morelli and Arciello (1952) found a significant increase in the plasma cells in

TABLE I

PRINCIPAL FINDINGS OF OTHER AUTHORS IN THE BONE MARROW OF RHEUMATOID ARTHRITIS

Subject	Date	Authors	No. of Cases	Principal Findings
Iron Content	1953	Smith	3	Stainable iron present in two cases and absent in one.
	1954	Pratt and Johnson	5	Iron content greater than normal in four cases.
Cytology	1938	Mester	33	Plasmacytosis.
	1938	Kaether	26	Toxic granulation of neutrophil polymorphs.
	1937	Michelazzi	1	Increase in reticulum cells and plasma cells.
	1940	Fleischhacker and Lachnit	55	Slight increase in plasma cells.
	1945	Merlo and Tortori-Donati	7	"Histiolymphocytosis".
	1946	Luchesi, Luchesi, and Da Silva	32	Plasmacytosis.
	1948	Marmont	21	Plasmacytosis. Eosinophilia. "Active reticulo-endothelial systems".
	1948	Nilsson	12	Disturbance of erythroid maturation.
	1949	Leitner	2	Plasmacytosis. Eosinophilia. Shift to left of myeloid series.
	1951	Hayhoe and Smith	10	Plasmacytosis in nine cases, associated with hyperglobulinaemia in six where plasma proteins were estimated.
	1951	Jasiński and Staehelin	20	Eosinophilia.
	1951	Finch, Crockett, Ross, and Bayles	—	Moderate depression of erythroid series.
	1952	Morelli and Arciello	15	Plasmacytosis in thirteen cases.
	1952	Edgcumbe and Husain	13	Normal plasma cells and eosinophils.
	1953a	Jeffrey	16	Plasmacytosis in only three cases. Low proportion of mature normoblasts in seven.
	1953	Klein and Block	8	Described plasmacytosis.
	1954	Houli and Monteiro Marinho	20	Plasmacytosis in only five cases. Eosinophilia 7.
	1955	Ebaugh, Peterson, Rodnan, and Bunim	21	Slight plasmacytosis.

thirteen of their fifteen cases. Although the total protein level in the plasma was normal in all their cases, the albumin/globulin ratio was near unity. Edgcumbe and Husain (1952) investigated thirteen cases. The number of plasma cells was normal in every one and there was no evidence of eosinophilia. Differential cell counts were made on the marrow in sixteen cases of rheumatoid arthritis by Jeffrey (1953a). In only three instances did he find an increase of plasma cells; in seven cases the proportion of mature normoblasts was reduced. In describing a series of cases in which hyperglobulinaemia was associated with plasmacytosis, Klein and Block (1953) mention eight cases of rheumatoid arthritis. Houli and Monteiro Marinho (1954) examined the marrow in twenty cases: the plasma cell count was raised in five, but bore no relationship to the results of plasma flocculation tests; seven cases showed eosinophilia. Ebaugh, Peterson, Rodnan, and Bunim (1955) discussed 21 cases; they gave no figures but found that a slight plasmacytosis was a constant feature.

The principal findings of previous authors are summarized in Table I. It is obvious that there is a divergence of views in respect of many features and that the characteristics of the bone marrow in rheumatoid disease have not been established.

Material

Marrow samples were obtained from 64 in-patients in the Rheumatic Unit of the Northern General Hospital, Edinburgh. In each case a firm diagnosis of rheumatoid arthritis had been reached on clinical and radiological grounds. Care was taken to exclude patients with iron deficiency due to blood loss. Marrow biopsy was usually performed during the first 2 weeks of the patients' stay in hospital. During this period all were receiving the same basic regime of treatment consisting of bed rest, salicylates, and physiotherapy.

The composition of the group with regard to sex, age, duration, and activity of the disease is shown in Table II. In assessing the activity of the disease the number of joints involved, the degree of systemic disturbance, the haemoglobin level, and the erythrocyte sedimentation rate (E.S.R.) were considered. Patients were graded as very active, moderately active, or inactive.

The peripheral blood was examined within 3 days of marrow biopsy. The plasma iron concentration was measured in 58 cases and in 49 the plasma proteins were estimated.

Methods

Marrow Biopsy.—The technique used for obtaining the marrow sample was that described by Davidson (1941). In most cases the bone was penetrated with unusual ease and adequate samples were obtained at the first attempt. 2 ml. blood and marrow particles were aspirated by brisk suction. The greater part of the specimen was added to a tube containing heparin powder, and the remainder was divided between a tube containing Wintrobe's anti-coagulant and a clean, dry watch glass. The heparinized sample was submitted to histological and chemical examination. Nucleated cell counts were performed on the oxalated sample. Particles picked from the watch glass were used for preparing smears.

TABLE II

COMPOSITION OF GROUP

Total Number of Cases		64
Sex	Male	26
	Female	38
Age Distribution (years)	20–39	7
	40–59	38
	60–79	19
	Mean 52·9	
Duration of Disease (years)	0–1·9	13
	2–9·9	28
	10 and Over	23
	Mean 8	
Activity of Disease	Very active	14
	Moderately active	47
	Inactive	3

Histology.—Marrow particles taken from the tube containing heparin were placed in a small glass bottle in which was 20 ml. fixative (Hutchison, 1953). After 1 to 2 hrs the material was transferred to a thin glass test-tube, dehydrated in changes of alcohol, cleared in chloroform, and embedded in paraffin wax. The marrow fragments were found at the apex of the hemispherical block obtained by breaking the test-tube. Multiple sections cut from each block were stained by haematoxylin and eosin, by the Prussian blue method for ferric iron, and by the method of Barrett (1944).

Sections stained with haematoxylin and eosin provided an index of the adequacy of the sample. The distribution and nature of the cells in thirty of the marrows was assessed on the sections stained by Barrett's method. The ferric iron content of the marrow was estimated by the Prussian blue reaction. Staining was performed in glass jars previously rendered iron free; experiment showed that optimum results were obtained by immersing sections for 15 min. at 56° C. in a freshly prepared mixture of 4 per cent. hydrochloric acid and 4 per cent. potassium ferrocyanide.

The amount of stainable ferric iron present in the sections was assessed as nil, a trace, one plus, or two pluses. Control material was provided by marrow obtained from cases of iron deficiency anaemia, pernicious anaemia, haemochromatosis, and poly-

cythaemia vera (Table III). In addition, marrow was aspirated at necropsy from five independent sites in each of two cases of rheumatoid disease. Estimates of the amount of iron in the individual aspirates in each instance gave good agreement.

Chemical Estimations of Non-Haem Iron in Bone Marrow.—A paper describing this method has been prepared for publication elsewhere and only a brief outline is given below:

All glassware and reagents were rendered iron-free.

The sample of marrow containing heparin as anticoagulant was used. Marrow particles were washed in 0·9 per cent. saline and transferred to an all-glass homogenizer containing 1 ml. distilled water. An even suspension of the tissue was made, the tube was rinsed with 0·5 ml. water, and the volume of the suspension was noted. A blank solution was prepared in the same way but omitting the marrow. All estimations were referred to this. Samples were taken for the estimation of iron and protein.

The iron was estimated by a method essentially that of Ramsay and Campbell (1954), using 1 ml. of the suspension and modifying the quantity of the other reagents to give a final volume of 3 ml. The protein was estimated in 0·2 ml. of the suspension, using the method of Lowry, Rosebrough, Farr, and Randall (1951), again modifying the quantity of the reagents to give a volume of 3 ml. All solutions were chilled and centrifuged in the cold to remove suspended material prior to colorimetric estimation.

The reproducibility of the method was tested by replicate estimations on a single sample. Six determinations were made giving a mean value of 0·45 μg. iron and a standard deviation of ±0·077 μg. The mean value for protein was 786 μg.±54.

The error in sampling was tested in two ways. One marrow sample was divided into four parts and each estimated separately. A mean value of 85 μg. iron/100 mg. protein was obtained with a range of 81–90 μg. At two separate necropsies three samples were obtained from the sternum and two from the iliac crest. A mean value of 45 μg./100 mg. (range 31–53 μg.) was obtained from the first case, and of 219 μg./100 mg. (range 197–240 μg.) from the second.

Myelogram.—Leishmann and Giemsa stains were used for staining marrow smears. In sixty cases the preparation was satisfactory and differential cell counts were made on 1,000 cells. Two observers (D.L.G. and J.R.) each counted 500 cells from a selection of two to four smears. The values given by Whitby and Britton (1953) for the normal myelogram were used for comparison. The differential cell counts in ten normal controls fell within these limits with one exception in which the plasma cell count reached 2·1 per cent. This figure was therefore taken as the upper limit of the normal range.

Peripheral Blood.—Blood was obtained by venepuncture and 3 ml. was mixed with Wintrobe's anticoagulant. In all cases the haemoglobin level, red cell count, E.S.R., and packed cell volume (P.C.V.) were estimated from this sample.

The haemoglobin level was measured colorimetrically by the alkaline haematin method of Clegg and King (1942) and compared with the artificial standard of Gibson and Harrison (1945).

Red cells were diluted with Hayem's solution in a standard red cell pipette and counted in a Neubauer chamber.

Westergren tubes were used for the estimation of the E.S.R. and the fall in mm. was read at the end of one hour.

The P.C.V. was measured in a M.S.E. haematocrit centrifuge after 30 min. at 3,000 r.p.m.

Plasma Iron.—The method used for measuring the plasma iron concentration was that described by Roy and others (1955).

Plasma Proteins.—These were estimated by the method of Gornall, Bardawill, and David (1949). The plasma protein levels of ten normal controls fell within the range given by these authors. The mean level of albumin was 4·77 g./100 ml. (standard deviation ±0·38), and of globulin 2·26 g./100 ml. (±0·16).

Results

Iron Content of Bone Marrow.—In 61 cases the iron content of the marrow was estimated by the

TABLE III

IRON CONTENT OF MARROW ESTIMATED BY PRUSSIAN BLUE REACTION IN TWELVE CASES WITH IRON DEFICIENCY OR EXCESS

Disease	No. of Cases	Histochemical Assessment of Iron Content of Marrow				
		Nil	Trace	+	++	+++
Iron Deficiency Anaemia	2	2	—	—	—	—
Pernicious Anaemia	4	—	—	—	3	1
Polycythaemia Vera	1	—	—	—	1	—
Haemochromatosis	5	—	—	—	2	3

Prussian blue reaction. In nineteen cases (31 per cent.) no stainable iron was found. In the other 42 cases (69 per cent.) iron was seen in varying amounts. The results are presented in Table IV. In six of the males (26 per cent.) and 13 of the females (34 per cent.) no stainable iron was seen.

TABLE IV
MARROW IRON ESTIMATED BY PRUSSIAN BLUE REACTION IN 61 CASES OF RHEUMATOID ARTHRITIS

Amount of Stainable Iron ..	Nil	Trace	+	++
Number of Cases	19	11	26	5

Marrow iron was estimated by the chemical method in 32 cases. In thirty of these the sample was divided and iron was estimated by the Prussian blue reaction and by the chemical method. The relationship between the results of the two methods is shown in Fig. 1. The mean of the chemical estimations in cases showing only a trace or no stainable iron is lower than the mean of those showing one or two pluses ($P=0{\cdot}05$).

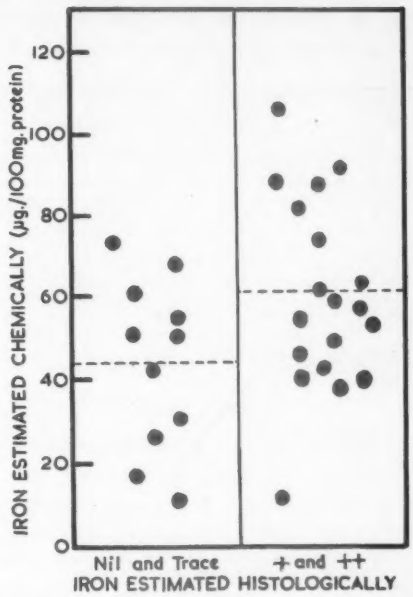


Fig. 1.—Comparison of iron estimations by chemical and histological methods.

Peripheral Blood.—Examination revealed a moderate degree of anaemia in most cases. The mean level of haemoglobin for the whole group was 11·5 g./100 ml. (78 per cent.). In 57 cases the red cells were normocytic and hypochromic. In three females microcytosis was present. In only five cases were the red cells normochromic. The average mean corpuscular volume (M.C.V.) for the whole group was 83·3 c.µ. and average mean corpuscular haemoglobin concentration (M.C.H.C.) 28·7 per cent.

The E.S.R. ranged from 3 to 108 mm./hr (mean 47 mm./hr).

The plasma iron concentration ranged from 24 to 146 µg./100 ml.

In the female patients anaemia was more severe and the disease more active than in the male patients. The mean values for haemoglobin, red cell count, mean corpuscular volume, mean corpuscular haemoglobin concentration, erythrocyte sedimentation rate, and plasma iron concentration for the two sexes are summarized in Table V.

Relationship between Amount of Iron in Marrow and Other Features of the Disease.—No relationship was found between the amount of iron in the marrow estimated histologically or chemically, and the haemoglobin level, red cell count, M.C.H.C., E.S.R., or plasma iron concentration. The results of this analysis are shown in Table VI (overleaf).

There was a tendency for stainable iron to be absent from the marrow more frequently as the duration of the disease increased. In the group of short duration (0–1·9 yrs), 18 per cent. had no iron in the marrow compared with 41 per cent. in the group where the duration of disease was 10 years

TABLE V
FINDINGS IN PERIPHERAL BLOOD OF 26 MALE AND 38 FEMALE CASES OF RHEUMATOID ARTHRITIS

Sex	No. of Cases	Peripheral Blood Values (Mean and Standard Deviation)					
		Hb. (g./100 ml.)	Red Cell Count (millions/c.mm.)	Mean Corpuscular Volume (cu.µ)	Mean Corpuscular Hb Concentration (g. per cent.)	Erythrocyte Sedimentation Rate (mm./hr.)	Plasma Iron (µg./100 ml.)
Males ..	26	12·4±1·2 (84 per cent.)	4·94±0·37	84·6±2·4	29·1±3·9	39±8	92±11 (23 cases)
Females	38	10·9±0·9 (73 per cent.)	4·94±0·56	82·4±3·6	28·7±4·9	52±7	80±29 (35 cases)

TABLE VI

RELATIONSHIP BETWEEN PERIPHERAL BLOOD VALUES AND IRON CONTENT OF MARROW*

Group	Stainable Iron	No. of Cases	Non-Haem Iron (μg./100 mg. protein)	Plasma Iron (μg./100 ml.)	Hb. (g./100 ml.)	Red Cell Counts (mill./c.mm.)	Erythrocyte Sedimentation Rate (mm./hr.)	Mean Corpuscular Haemoglobin Concentration (g. per cent.)
I	++	5	—	89	11·2	4·33	66	32·0
		5	66	89	11·2	4·33	66	32·0
II	+	26	—	89	11·7	4·77	46	29·4
		15	58	84	11·7	4·85	42	28·4
Mean Values for Cases in Groups I and II		31	—	89	11·6	4·70	49	29·8
		20	61	85	11·6	4·72	48	29·3
III	Trace	11	—	93	11·7	4·83	40	28·7
		4	42	88	11·7	4·80	36	28·9
IV	Nil	19	—	77	11·2	4·69	47	28·9
		7	47	73	11·7	4·74	35	29·8
Mean Values for Cases in Groups III and IV		30	—	83	11·4	4·74	44	28·9
		11	45	78	11·7	4·76	35	29·5

* In each group the mean values for all cases are given by the upper line of figures; the lower line gives the values for cases in which both histological and chemical estimates of iron were made.

or longer. 29 per cent. of the intermediate group showed no stainable iron.

It was also found that, although the plasma iron concentration was subnormal, the level could not be clearly related to any other feature of the disease.

When the haemoglobin level was related to the E.S.R. there was a highly significant correlation between the degree of anaemia and the activity of the disease ($r=0·474$; S.E. of $r=0·126$; $P<0·01$). In 35 cases the peripheral blood had been examined on three occasions during the four weeks before marrow biopsy. When the average haemoglobin and average E.S.R. for these cases were compared the correlation was confirmed.

Cytology of Marrow.—The architecture of the marrow was normal. There was no histological evidence of hyperplasia of the reticulo-endothelial system.

Examination of the marrow smears confirmed that the samples were of normal cellularity.

Myeloid Series.—The total neutrophil count (neutrophil precursors and neutrophil polymorphs) ranged from 43·2 to 74·1 per cent. (normal range 22–73 per cent.). In one case only was the upper normal limit exceeded. There was no evidence of any disturbance of white cell formation or maturation.

The total eosinophil count (eosinophil precursors and eosinophil polymorphs) was above the upper limit of normal (7·5 per cent.) in five cases (8·5 per cent.). In these five cases the counts ranged from 8·1 to 12·7 per cent.

Erythroid Series.—The total normoblast count (early, intermediate, and late) ranged from 10·0 to 46·8 per cent. (normal range 11 to 34 per cent.). In sixteen cases (27 per cent.) the proportion of normoblasts exceeded 34 per cent., but in only five did the count exceed 40 per cent. In these sixteen cases the myeloid/erythroid ratio was less than 2:1.

In two cases macronormoblasts were seen. Neither case had macrocytosis or evidence of folic acid or vitamin B_{12} deficiency. In the whole group no other abnormality of maturation was observed, nor was any disturbance of haemoglobinization recognized. Examination of the total normoblast count in those cases which had received gold (32 cases) or phenylbutazone (eleven cases) revealed no evidence that previous treatment with these drugs had influenced normoblast development.

Plasma Cells.—The plasma cell count ranged from 0 to 5 per cent. (normal range 0 to 2·1 per cent.) and in 21 cases (35 per cent.) the number of plasma cells exceeded 2·1 per cent.

In the 49 cases where the plasma proteins were

estimated, the mean albumin level was 3·73 g./100 ml. (standard deviation ±0·49) and the mean globulin level 2·43 g./100 ml. (±0·43).

Relationship of Cytology of Marrow to Other Features of the Disease.—Normoblastosis or eosinophilia or plasmacytosis was not related to the degree of anaemia, the activity of the disease, the plasma iron level, or the iron content of the marrow.

Although the total normoblast count for most cases was within the normal range, it was found that the haemoglobin level tended to be low when the normoblast count was low. This association was clearer when the cases of short duration (0 to 1·9 years) were excluded. For the 48 cases in the groups of intermediate and long duration there was a highly significant correlation between the haemoglobin level and the total normoblast count ($r=0·467$; S.E. of $r=0$ is 0·144; $P<0·01$).

For the 45 cases where both values were available, there was a highly significant correlation between the plasma cell count in the marrow and the globulin level in the plasma ($r=0·479$; S.E. of $r=0$ is 0·150; $P<0·01$) (Fig. 2).

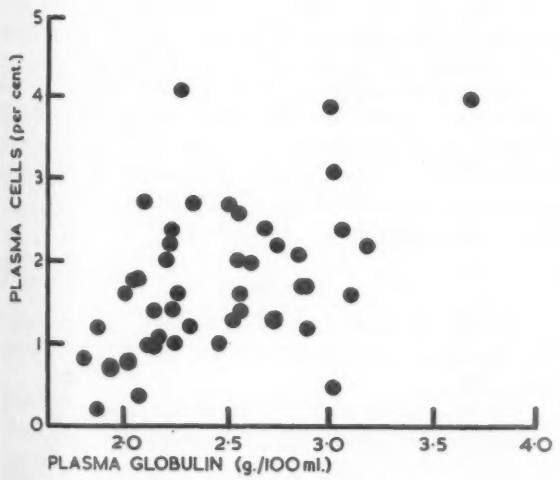


Fig. 2.—Relationship between plasma cell count in marrow and plasma globulin level.

The number of plasma cells was not related to the degree of anaemia or to the activity of the disease. There was, however, a definite tendency for the plasma cell count to fall as the duration of the disease increased. The mean plasma cell count for the early group (0–1·9 yrs) was 2·6 per cent., for the intermediate group (2–9 yrs) 1·72 per cent., and for the group of long duration (10 yrs and over) 1·34 per cent. The association between the plasma cells and the duration of the disease is shown in Table VII.

TABLE VII

EFFECT OF DURATION OF DISEASE ON PLASMA CELL COUNT IN BONE MARROW IN SIXTY CASES OF RHEUMATOID ARTHRITIS

Duration of Disease (years) ..	0–1·9	2–9·9	10 and Over
Mean Plasma Cell Count (per cent.)	2·6	1·7	1·3
Standard Error of Mean	0·344	0·172	0·193
Number of Cases	12	26	22

Discussion

A review of the literature provides little information as to the iron content of the marrow in rheumatoid arthritis. In anaemia arising from iron deficiency it is generally accepted that iron in the form demonstrated by the Prussian blue staining reaction is absent from the marrow, and it has been stated (Hutchison, 1953) that the administration of iron is of benefit only in these conditions. Certain features, such as persistent hypochromia of the red cell and low plasma iron values, have suggested that a deficiency of iron may play a part in the production of the anaemia of rheumatoid arthritis. This view receives some support from the reports of improvement in the anaemia following the administration of large doses of iron by the intravenous route. In anaemia due to other causes, such as infection, malignant disease, and uraemia, however, the amount of iron in the marrow tends to be greater than normal while the level in the plasma is frequently below normal. Since there is no evidence that absorption of iron from the gut is impaired in rheumatoid arthritis, or that it is excreted in abnormal amounts, there seems no reason to suppose that stores of iron in the body would be inadequate.

An attempt has therefore been made in the present investigation to determine the iron content of the marrow in a large group of patients.

Marrow iron was estimated in 61 cases by the Prussian blue reaction. In nineteen cases (31 per cent.) no stainable iron could be demonstrated microscopically. Of these, six were male and thirteen female. In a further eleven cases only traces of iron were present. Marrow iron was also estimated by the chemical method in thirty cases and, although measurable amounts were found in all, a rough correlation existed between the results of the two methods. It must be borne in mind that, whereas the staining reaction only reveals iron in the form of haemosiderin, the chemical method measures all the non-haem iron in the sample.

No correlation could be demonstrated between the presence or absence of stainable iron in the marrow or the amount estimated chemically and the haemoglobin level, erythrocyte count, mean corpuscular haemoglobin concentration, erythrocyte sedimentation rate, or plasma iron concentration. This lack of correlation suggests that deficiency of iron in the marrow is not an important factor in the causation of anaemia in rheumatoid arthritis. On the other hand, there was a highly significant correlation between the E.S.R. and haemoglobin level. Protein and porphyrin metabolism may be profoundly altered in rheumatoid arthritis (Jeffrey, 1953b). Hypochromia of the red cells could therefore arise from factors other than inadequate supplies of iron. The improvement in the anaemia which follows the administration of cortisone or corticotrophin without additional iron therapy would favour this idea.

The cytological pattern of the bone marrow was examined in sixty cases and did not differ significantly from normal. No evidence has been obtained to support the views of those authors who have described various abnormalities as characteristic of the marrow in this disease.

In 35 per cent. of cases there was a slight increase in the proportion of plasma cells. Plasmacytosis of similar degree occurs in many diseases and is commonly associated with conditions where the production of antibodies is increased (Marshall, 1956). A highly significant correlation was found in this series of cases between the marrow plasma cell count and the level of globulin in the plasma, but there is not as yet any evidence of increased production of antibodies in rheumatoid arthritis. In contrast to the finding of Hayhoe and Smith (1951) hyperglobulinaemia was not constantly associated with plasmacytosis.

No abnormal changes in the myeloid cell series were found. The five patients in whom eosinophilia was demonstrated differed in no other way from the remainder of the group. It is of interest that eosinophilia in the bone marrow in rheumatoid arthritis has been reported most frequently from countries where parasitic disease is endemic.

Alexander, Richmond, Roy, and Duthie (1956) state that an unusually rapid rate of destruction of circulating red cells may be a factor in the production of anaemia in rheumatoid arthritis. In a study of the erythroid cell series in the marrow, it was found that there was a slight increase in the proportion of normoblasts in 27 per cent. of cases, while in the remainder the normoblast count was within the normal range. In contrast to the findings when anaemia is due to increased blood destruction, there was a direct relationship between the haemoglobin level and the normoblast count, suggesting an inadequate normoblast response in the anaemia of this disease. This association became highly significant when cases of less than 2 years duration were excluded. It would appear from this that inadequate formation of normoblasts is more pronounced in the later stages of the disease. Disturbance of the maturation of erythroid precursors has been described by Nilsson (1948) and Jeffrey (1953a), but such changes were not observed in the present series, nor was frank hypoplasia found in any case.

It becomes apparent that anaemia in rheumatoid arthritis is likely to arise from more than one cause. It bears a significant relationship to the activity of the disease. It is associated with, but not directly due to, a disturbance of iron metabolism. While the iron content of the marrow was low in half of the cases which have been studied, iron was present in the remainder in easily measurable amounts. Persistent hypochromia of erythrocytes is evidence of a disturbance in haemoglobin synthesis. An increased rate of red cell destruction may contribute to the anaemia, and it appears that the normoblast response is inadequate, particularly in the later stages of the disease. The role of iron is difficult to evaluate. The iron content of the marrow was frequently low, but it could not be related to the peripheral blood findings and therefore did not appear to be an important factor in the production of anaemia. Improvement in the anaemia has been shown to follow the use of iron intravenously, but its mode of action is not yet clear.

Summary

(1) The iron content and cytology of the sternal marrow has been examined in 64 cases of rheumatoid arthritis.

(2) In 31 per cent. of cases no iron could be demonstrated by the Prussian blue method.

(3) Marrow iron was estimated by a chemical method in 32 instances. Iron in measurable amounts was present in all the specimens examined.

(4) No relationship was demonstrable between the amount of iron in the marrow, estimated by the two methods, and the haemoglobin level, erythrocyte count, mean corpuscular haemoglobin concentration, erythrocyte sedimentation rate, or plasma iron level.

(5) There was a highly significant correlation between the haemoglobin level and the erythrocyte sedimentation level.

(6) Examination of the cytology of the marrow revealed no significant abnormality. In 35 per

cent. of cases there was a slight increase in the proportion of plasma cells. When all the cases in the series were considered, there was a significant relationship between the proportion of plasma cells and the level of globulin in the serum.

(7) The proportion of normoblasts was directly related to the haemoglobin level, especially in cases of more than 2 years' duration, suggesting a failure of the marrow to respond to the anaemia.

(8) It would appear that, although the degree of anaemia in rheumatoid arthritis is related to the activity of the disease, it does not arise directly from a deficiency of iron in the marrow. Other factors, such as increased destruction of red cells, depression of the formation of red cell precursors, and impaired synthesis of haemoglobin, may be important.

We wish to express our thanks to Dr. P. E. Brown, of the Department of Public Health and Social Medicine, Edinburgh University, and to Dr. J. L. Potter, Nuffield Research Fellow, for statistical help, and to Miss Dorothy Anderson, haematological technician, for her accurate work throughout this investigation.

Throughout the period when this work was done, the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company.

REFERENCES

Alexander, W. R. M., Richmond, J., Roy, L. M. H., and Duthie, J. J. R. (1956). *Annals of the Rheumatic Diseases*, **15**, 12.
Barrett, A. M. (1944). *J. Path. Bact.*, **56**, 133.
Clegg, J. W., and King, E. J. (1942). *Brit. med. J.*, **2**, 329.
Davidson, L. S. P. (1941). *Edinb. med. J.*, **48**, 678.
Davidson, W. M., and Jennison, R. F. (1952). *J. clin. Path.*, **5**, 281.
Ebaugh, F. G., Peterson, R. E., Rodnan, G. P., and Bunim, J. J. (1955). *Med. clin. N. Amer.*, **39**, 489.
Edgcumbe, J. O. P., and Husain, O. A. N. (1952). *Annals of the Rheumatic Diseases*, **11**, 257.
Finch, S. C., Crockett, C. L., Ross, J. F., and Bayles, T. B. (1951). *Blood*, **6**, 1034.
Fleischhacker, H., and Lachnit, V. (1940). *Wien. klin. Wschr.*, 53, 189.
Gibson, Q. H., and Harrison, D. C. (1945). *Biochem. J.*, **39**, 490.
Gornall, A. G., Bardawill, C. J., and David, M. M. (1949). *J. biol. Chem.*, **177**, 751.
Hayhoe, F. G. J., and Smith, D. Robertson (1951). *J. clin. Path.*, **4**, 47.
Houli, J., and Monteiro Marinho, H. (1954). *Annals of the Rheumatic Diseases*, **13**, 327.
Hutchison, H. E. (1953). *Blood*, **8**, 236.
Jasiński, B., and Staehelin, A. (1951). *Schweiz. med. Wschr.*, 81, 619.
Jeffrey, M. R. (1952). *Annals of the Rheumatic Diseases*, **11**, 162.
—— (1953a). *Blood*, **8**, 502.
—— (1953b). *Brit. med. J.*, **2**, 912.
Kaether, H. (1938). *Z. Rheumaforsch.*, **1**, 473.
Klein, H., and Block, M. (1953). *Blood*, **8**, 1034.
Leitner, S. J. (1949). "Bone Marrow Biopsy", Engl. trans. by C. W. C. Britton and E. Neumark. Churchill, London.
Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). *J. biol. Chem.*, **193**, 265.
Luchesi, M., Luchesi, O., and Da Silva, M. P. (1946). *Rev. argent. Reum.*, **10**, 294.
Marmont, A. (1948). *Arch. "Maragliano" Patol. Clin.*, **3**, 1289.
Marshall, A. H. E. (1956). "An Outline of the Cytology and Pathology of the Reticular Tissue". Oliver and Boyd, Edinburgh.
Masshoff, W., and Gruner, P. (1951). *Acta haemat. (Basel)*, **5**, 19.
Merlo, P., and Tortori-Donati, B. (1945). *Rass. Fisiopat. clin. ter.*, **17**, Suppl. 2, p. 37.
Mester, A. (1938). *Z. Rheumaforsch.*, **1**, 535.
Michelazzi, A. M. (1937). *Minerva med. (Torino)*, **28**, (2) 609. (Quoted in *J. Amer. med. Ass.* (1938), **110**, 404.)
Morelli, A., and Arciello, G. (1952). *Riform. med.*, **66**, 620.
Nilsson, F. (1948). *Acta med. scand.*, Suppl. 210.
Pratt, P. T., and Johnson, M. E. (1954). *Arch. intern. Med.*, **93**, 725.
Ramsay, W. N. M., and Campbell, E. A. (1954). *Biochem. J.*, **58**, 313.
Rath, C. E., and Finch, C. A. (1948). *J. Lab. clin. Med.*, **33**, 81.
Ross, D. N. (1950). *Annals of the Rheumatic Diseases*, **9**, 358.
Roy, L. M. H., Alexander, W. R. M., and Duthie, J. J. R. (1955). *Ibid.*, **14**, 63.
Sinclair, R. J. G., and Duthie, J. J. R. (1949). *Lancet*, **2**, 646.
——, —— (1950). *Brit. med. J.*, **2**, 1257.
Smith, M. D. (1953). *Glasg. med. J.*, **34**, 41.
Stevens, A. R., Jr., Coleman, D. H., and Finch, C. A. (1953). *Ann. intern. Med.*, **38**, 199.
Whitby, L. E. H., and Britton, C. J. C. (1953). "Disorders of the Blood", 7th ed. Churchill, London.

Nature de l'anémie dans l'arthrite rhumatismale. III. Altérations de la moelle osseuse et leurs relations avec les autres caractères de la maladie

RÉSUMÉ

(1) La teneur en fer et la cytologie de la moelle sternale furent examinées dans 64 cas d'arthrite rhumatismale.

(2) Dans 31 pour cent des cas on ne décela pas de fer par la méthode du bleu de Prusse.

(3) Le fer dans la moelle fut dosé par une méthode chimique dans 32 cas. Du fer en quantités mesurables fut trouvé dans tous les prélèvements.

(4) Aucun rapport ne fut démontrable entre la quantité de fer dans la moelle, déterminée par les deux méthodes, et le taux d'hémoglobine, la numération érythrocytaire, la valeur globulaire, la vitesse de sédimentation érythrocytaire ou le taux de fer plasmatique.

(5) Il y avait une corrélation très significative entre le taux d'hémoglobine et la vitesse de sédimentation globulaire.

(6) L'examen cytologique de la moelle ne révéla aucune anomalie significative. Dans 35 pour cent des cas il y eut une légère augmentation du nombre des cellules plasmatiques. Quand tous les cas de la série furent considérés, on constata une relation significative entre le nombre des cellules du plasma et le taux d'hémoglobine sérique.

(7) La proportion des normoblastes était directment liée au taux d'hémoglobine, en particulier dans les cas remontant à plus de deux ans, ce qui suggère une défection de la moelle devant l'anémie.

(8) Il semblerait que, bien que le degré d'anémie dans l'arthrite rhumatismale soit lié à l'activité de la maladie, il ne découle pas directement d'une carence de fer dans la moelle. D'autres facteurs, tels que destruction accrue des hématies, entrave à la formation des précurseurs des hématies et synthèse diminuée de l'hémoglobine, peuvent être importants.

La naturaleza de la anemia en la artritis reumatoide III. Alteraciones de la médula ósea y sus relaciones con otros caracteres de la enfermedad

SUMARIO

(1) Se investigaron el contenido de hierro y la citología de la médula esternal en 64 casos de artritis reumatoide.

(2) En el 31% de los casos no se pudo demostrar presencia de hierro por el método de azúl de Prusia.

(3) Se procedió al dosaje de hierro en la médula por un método químico en 32 casos, encontrándole en cantidades mensurables en todos los espécimenes.

(4) No se evidenció relación alguna entre la cantidad de hierro en la médula, determinada por ambos métodos, y las cifras de hemoglobina, de los ertrocitos, la concentración corpuscular media de hemoglobina, la

velocidad de sedimentación eritrocitaria y la cifra de hierro plasmático.

(5) Se encontró correlación muy significativa entre las cifras de hemoglobina y la velocidad de sedimentación globular.

(6) La investigación citológica de la médula no evidenció anomalías significativas. En un 35% de los casos hubo una pequeña aumentación de la cifra de células plasmáticas. Al considerar todos los casos de la serie, se halló una relación significativa entre las cifras de las células del plasma y las de hemoglobina sérica.

(7) Hubo relación directa entre la proporción de normoblastos y las cifras de hemoglobina, en particular en los casos de más de dos años de duración, lo que sugiere la falla de la médula en responder a la anemia.

(8) Parece pues que, aunque el grado de anemia en la artritis reumatoide esté ligado a la actividad mórbida, éste no procede directamente de una carencia de hierro en la médula. Otros factores, tales como destrucción más rápida de eritrocitos, impedimento en la formación de sus precursores y síntesis disminuida de hemoglobina pueden tener importancia.

Ann. rheum. Dis. (1956), **15**, 227.

USE OF THE HYPOSPRAY JET INJECTOR FOR THE INTRA-ARTICULAR AND LOCAL ADMINISTRATION OF HYDROCORTISONE ACETATE*

BY

MORRIS ZIFF†, VINCENT CONTRERAS‡, AND FRANK R. SCHMID§

From the Department of Medicine and the Study Group on Rheumatic Diseases
New York University College of Medicine, New York City

(RECEIVED FOR PUBLICATION JUNE 11, 1956)

The local treatment of rheumatoid arthritis with hydrocortisone acetate was first described by Hollander (Hollander, Brown, Jessar, and Brown, 1951). Improvement was paralleled by reduction of inflammation and by the return of the properties of the synovial fluid towards normal (Ziff, Scull, Ford, McEwen, and Bunim, 1952). It is the purpose of this paper to present the experience of the authors using a hypospray jet injector for the intra-articular and local injection of hydrocortisone acetate, since this instrument offers certain advantages which will be described.

Material and Methods

The hypospray jet injector¶ (Figge and Barnett, 1948; Hughes, Jordan, and Hill, 1949) was designed to introduce substances under pressure either subcutaneously or intramuscularly without using a needle (Fig. 1). Its use has been extended to the intra-articular and local injection of hydrocortisone acetate in the present investigation; 1 ml. of the material to be injected is contained in metapules, which are small metal cartridges, hermetically sealed in a sterile aluminium container. The mechanism employed to force the medication through the skin is a spring-activated plunger which forces the contents of the metapule through a minute opening in a fine jet. An adjustment sleeve on the instrument permits the injection of 1 ml. or an accurate fraction of this amount (0·6 to 0·9 ml.). No sterilization of the instrument is necessary, because no part of it comes into contact with the sterile materials being injected. Only the skin at the site of injection and the nozzle of the injector need be wiped with alcohol. All injections in the present study were made at maximum spring tension.

Early trials of intra-articular injection were carried out using a standard instrument supplied by the manufacturer, but subsequently a special injector, approximately 18 per cent. more energetic, was made available.

* This work was supported by a grant from the Masonic Foundation for Medical Research and Human Welfare.
† Senior Fellow, Arthritis and Rheumatism Foundation.
‡ Rockefeller Foundation Fellow. Present address: Universidad de Chile, Santiago, Chile.
§ Trainee, National Institute of Arthritis and Metabolic Diseases, United States Public Health Service.
¶ This was obtained from the R. P. Scherer Corp., Detroit, Michigan, through the co-operation of Dr. Alpert, Medical Division, Merck and Co. Inc., Rahway, New Jersey. The hydrocortisone acetate contained in the metapules was provided by Merck and Co. Inc.

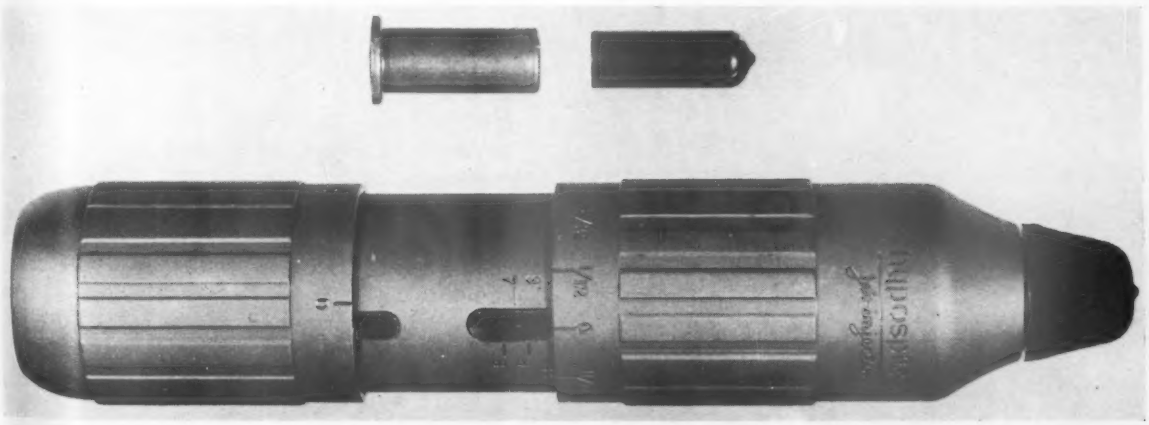


Fig. 1.—Hypospray jet injector, metapule, and cartridge.

In this report, the terms "standard" and "special" instrument are used to refer to these two models.

Anatomical and Radiological Studies

Various joints of an unembalmed cadaver were injected by hypospray, using the special instrument and metapules containing trypan blue. The joint was opened within a few minutes after injection at a site opposite to the point of injection. An assessment of the amount of dye in the peri-articular and articular structures and of the degree of penetration of the dye was made (Table I).

TABLE I

INJECTION OF TRYPAN BLUE INTO JOINTS OF A CADAVER

Joint	Amount Injected (ml.)	No. of Joints Injected	Dye found in Synovial Cavity (No. of Joints)
Proximal interphalangeal	0·6	5	4
Metacarpophalangeal ..	0·6	6	6
Wrist	1·0	2	2
Elbow	1·0	2	1
Ankle	1·0	2	2
Shoulder	1·0	2	2

In all instances the dye was observed to be deposited to some extent in the subcutaneous tissues, especially around the joint capsule.

The synovial cavities of seventeen of nineteen joints injected, however, contained the major portion of the injected dye. When dye was seen in the joint (Fig. 2), it was always present there in greater amounts than in the surrounding tissue.

Diodrast was injected by hypospray into several joints of four patients. These included proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, and knee joints. *X*-ray films in several planes were made within several minutes after injection to determine the course of the dye in the tissues. It was seen that in all these joints a portion of the dye entered the joint cavity and that the remainder was deposited peri-articularly. This is demonstrated in a proximal interphalangeal joint in Fig. 3 (opposite).

On the basis of experience with trypan blue and diodrast, the following techniques for hypospray injection were used in the trials reported in this paper. The joint was first palpated to determine the location of the joint space. Vessels and tendons were avoided where possible. The PIP, MCP, and metatarsalphalangeal (MTP) joints were injected either medially or laterally to the extensor tendon. The wrist was injected on the dorsal surface, distally and medially to the styloid process of the ulna in the small depression normally present in this area. The elbow was injected between the head of the radius and the olecranon process while holding the joint

Fig. 2.—Trypan blue in the dissected metacarpophalangeal joint spaces of cadaver after injection by hypospray.

Fig. 3.—Antero-posterior and lateral views of a proximal interphalangeal joint injected with diodrast by hypospray.

in 90° of flexion. The knee was injected from the medial aspect of the patella, at the mid-patellar level. Manually raising the patella by depressing the lateral edge was of assistance.

In all injections the nozzle of the instrument was held at the injection site with firm and steady pressure to avoid sliding of the instrument and consequent tearing of the skin by the fluid spray. After the injection had been given, the hypospray was held in place for a few seconds to diminish the possibility of subsequent bleeding.

Recovery Studies

To determine the extent to which the inoculum entered the joint space, experiments on recovery of injected steroid and trypan blue were performed. These were carried out in elbow and knee joints which contained effusions. The joint in each case was first entered by needle and a sample of control fluid was aspirated. The needle was then left in place, and at a point distant from the needle, either hydrocortisone acetate or trypan blue dye was injected by means of the hypospray (special instrument). The joint was then aspirated as completely as possible, either immediately or after a brief period of massage. When 1 ml. trypan blue solution was injected (Table II), the aspirated joint fluid was found to contain 59·6 per cent. of the injected dye in the case of the elbow, and 34·5 per cent. in the case of the knee, as determined spectrophotometrically. When 25 mg. hydrocortisone acetate were injected into the elbow and knee respectively, assay of the joint fluid obtained by aspiration, using a modified Porter-Silber method (Silber and Porter, 1954), demonstrated 13·6 per cent. of the injected material in the fluid from the elbow and 1·2 per cent. in the fluid from the knee. Presumably most of the remainder of the material was deposited in the synovial membrane and periarticular structures.

TABLE II

RECOVERY OF TRYPAN BLUE AND HYDROCORTISONE ACETATE FROM THE JOINT CAVITY AFTER INJECTION

Patient*	Joint	Material Injected	Per cent. Recovered
No. 1.	Elbow	Trypan Blue	59·6
2.	Knee		34·5
1.	Elbow	Hydrocortisone Acetate ..	13·6
3.	Knee		1·2

Clinical Studies

Clinical studies were carried out mainly in patients with rheumatoid arthritis. These included 33 females and nineteen males, ranging in age from 4 to 65 years.

In addition, the following patients were treated: osteo-arthritis, 3; gout, 1; Reiter's syndrome, 1; non-articular rheumatic conditions, 14.

The small joints were injected with 15 mg. hydrocortisone acetate in a volume of 0·6 ml., the wrist with 25 mg. in 1 ml., and the knee with 25 or 50 mg. in a 1 or 2 ml. volume. The total number of joint injections was 178.

In cases in which moderate improvement had taken place, a second and, in a few instances, a third and fourth injection were given. Each joint was examined at intervals after injection, usually within 4 days. The examination included an evaluation of pain, tenderness, swelling, effusion, heat, stiffness, and the range of motion in degrees. Swelling of the PIP joints was measured using a conventional set of jeweller's rings. Strength of hand-grip was measured by means of maximum squeeze on a rolled sphygmomanometer cuff inflated initially to 60 mm.

Hg. Wrist strength was measured on a specially constructed board on which the pressure exerted by the palm pressing a hinged lever against a sphygmomanometer cuff, initially inflated to 60 mm. Hg, was recorded. The result of each injection, or series of injections, was graded 1 to 4, Grade 1 indicating complete remission, Grade 2 major improvement, Grade 3 minor improvement, and Grade 4 no improvement or worsening.

Table III presents the data obtained on injection of the small joints of the hand, wrist, elbow, and knee, with both the standard and special instruments. It is seen that fourteen of 34 (41 per cent.) and 81 of 123 (66 per cent.) of the joints injected with the standard and special instruments respectively, showed major improvement or better (Grades 1 and 2). With the special instrument, marked improvement was observed in 42 of 49 PIP and MCP joints (86 per cent.), fourteen of 33 wrist joints (42 per cent.), and 23 of 39 knee joints (59 per cent.).

TABLE III

GRADE OF IMPROVEMENT OF RHEUMATOID JOINTS AFTER INJECTION WITH HYDROCORTISONE ACETATE

Instrument	Grade of Improvement	No. of Joints				Total
		PIP and MCP	Wrist	Knee	Elbow	
Standard	1	1	0	0	0	1
	2	5	8	0	0	13
	3	2	6	0	4	12
	4	1	7	0	0	8
	Total	9	21	0	4	34
Special	1	17	3	3	1	24
	2	25	11	20	1	57
	3	6	16	13	0	35
	4	1	3	3	0	7
	Total	49	33	39	2	123

In fourteen patients, nineteen joints (PIP, MCP, and wrist) were injected repeatedly, on the average three times, at 3-7 to 7-day intervals. In seven of these joints, repeated injections produced further improvement over that following the initial injection.

As a control for the injection of hydrocortisone, single injections of saline were given into PIP and wrist joints, and in one case into the elbow joint, simultaneously with injection of hydrocortisone acetate into homologous or contralateral joints of similar states of inflammation. The patients were unaware of the substitution. Using the standard injector, six of twelve joints showed major improvement or better when injected with hydrocortisone acetate, while only one of twelve showed similar improvement when injected with saline. Using the special instrument, eight of twelve joints showed major improvement when injected with hydrocortisone, while none showed similar improvement after saline injection, although three of the patients described subjective improvement.

Table IV shows a comparison of measurements after the injection of hydrocortisone acetate and saline respectively into contralateral wrist joints of the same patient. It is seen that though the hydrocortisone-injected wrist improved markedly, the wrist which was injected with saline showed no improvement.

In three patients with osteo-arthritis and synovitis, involving in one instance the knee and in two the PIP joints, in one patient with gouty arthritis of a knee, and in one with Reiter's syndrome involving the wrist, hypospray injection was followed by major improvement in each case.

Our experience with the treatment of non-articular rheumatism has been brief. Injections were usually made at the site of maximum tenderness. Four of six patients with acute subdeltoid bursitis were strikingly improved within 24 hours after two injections of 25 mg. hydrocortisone acetate given one immediately after the other. One patient

TABLE IV

COMPARISON OF EFFECTS OF INJECTION OF HYDROCORTISONE ACETATE AND SALINE INTO WRISTS (MALE, AGED 55, RHEUMATOID ARTHRITIS)

Wrist	Injection		Circumference (inches)	Tenderness	Effusion	Pain on Motion	Flexion	Extension	Grip (mm. Hg)	Wrist Pressure (mm. Hg)
Right	Hydrocortisone	Before ..	9·2	3+	4+	2+	20°	40°	125	110
		After* ..	8·0	±	2+	1+	45°	45°	150	140
Left	Saline	Before ..	8·5	3+	3+	2+	45°	45°	130	110
		After* ..	8·5	3+	3+	2+	30°	45°	130	140

* 4 days after injection.

with non-specific tenosynovitis of the extensor tendons of the foot, and five with rheumatoid tenosynovitis of a flexor tendon of the hand obtained prompt relief of pain within 24 hours. Three of the latter group, who had flexion contractures of approximately 10 to 30° at the MCP joint, were completely relieved within 3 days with restoration of full extension. One patient with De Quervain's syndrome showed marked improvement within the same period of time.

Undesirable Effects

No serious undesirable effects have resulted from the hypospray injections. Some relatively minor complications should, however, be pointed out. Practically all of the patients who received injections over the joint had some degree of discomfort at the moment of injection. This was described as a sudden, sharp, or burning sensation. The first injection was generally more uncomfortable than succeeding ones, since, presumably much of the discomfort was due to the element of surprise. In about one-third of the patients, the post-injection pain was severe enough to cause the subject to complain for periods up to a few minutes after the injection. Injection of the PIP and MCP joints was less well tolerated than injection of the large joints. This was very likely related in part to the sudden distension of a relatively small intra-articular and peri-articular space by the fluid injected, and in part to trauma to the periosteum created by the jet. In no case was pain a reason for discontinuing treatment when subsequent improvement occurred.

The authors have on a number of occasions injected their own normal joints and confirmed these observations. The discomfort at the moment of injection proved relatively slight; mild pain on motion and stiffness persisted for about 24 hours.

Six instances of minor ecchymosis at the site of injection were recorded. In one patient who was injected in the wrist, there developed an area of numbness about 1 cm. in diameter on the dorsum of the hand, which has continued to be present for 7 months. In another, injection on the lateral aspect of the knee was followed by bleeding from a small subcutaneous artery which was halted within a minute or two by application of a pressure bandage. In no instance did infection or worsening of the joint follow the injection of hydrocortisone.

Discussion

On the basis of direct observation of injected material in the joint and recovery from the joint fluid, and on the basis of clinical evaluation, it appears that penetration of the joint by hypospray injection did occur. It is also apparent that not all of the injected material entered the joint cavity. *X*-ray evidence indicated that that portion of the material which did not enter the joint was deposited in and about the peri-articular tissues in close proximity to the joint. While it is likely that penetration of the articular space is essential for a good therapeutic result, it seems probable that material deposited diffusely in and around the inflamed synovial membrane and joint capsule would also exert a beneficial effect. In the treatment of non-articular rheumatism, such as peri-arthritis and tenosynovitis, the value of the local infiltration of hydrocortisone is well recognized. Since the inflammation in rheumatoid arthritis is often peri-articular, the tendency of the hypospray jet to spread in the peri-articular tissue may be advantageous. Certainly, the results of the clinical trials recorded in this report are encouraging and compare favourably with those reported by needle injection (Hollander, Brown, and Jessar, 1954).

A practical feature of the hypospray injection is the simplicity of the technique. The physician can inject several joints in a short time without the preliminary preparation required for needle injection. In the experience of the authors, most of the patients who had had previous injections by needle preferred the hypospray.

Indications for use of the hypospray appear to be the same as for intra-articular injection by needle. The joint to be injected should be actively inflamed. Where irreversible damage is a major cause of disability little improvement may be expected, nor is the procedure warranted in the presence of generalized joint involvement. It must also be pointed out that the hypospray procedure has the disadvantage that it does not permit the withdrawal of fluid for diagnostic or therapeutic purposes. For injection of the hip, which it is not possible to penetrate by hypospray, the needle injection procedure remains the only one available. We have had no experience with injection of the shoulder joint.

Most of the results reported here refer to patients with rheumatoid arthritis, but the method has proved useful in other conditions known to be benefited by local hydrocortisone injection. The data obtained indicate that injection of the smaller joints results in a higher incidence of improvement than in the case of larger joints such as the wrist and the knee. This is probably due to the fact that the peri-articular structures of the smaller joints are more easily penetrated.

Summary

The hypospray jet injector has been applied to intra-articular injection. On the basis of recovery

of injected trypan blue and hydrocortisone acetate in the synovial fluid, it appeared that a significant portion of injected material penetrated the joint cavity. Radiological studies after the injection of diodrast demonstrated the dye both intra-articularly and peri-articularly.

Injections were made with both a standard instrument and a more energetic jet injector. With the latter, 66 per cent. of 123 injections of various joints of patients with rheumatoid arthritis showed major improvement. A small group of patients with other types of arthritis and with non-articular rheumatism were also treated with good results. The small joints of the hands obtained the most benefit.

The hypospray injection technique is simple and the procedure convenient. No serious complications have resulted.

REFERENCES

Figge, F. H. J., and Barnett, D. J. (1948). *Amer. Pract.*, 3, 197.
Hollander, J. L., Brown, E. M., Jr., and Jessar, R. A. (1954). *Med. Clin. N. Amer.*, 38, 349.
——, ——, ——, and Brown, C. Y. (1951). *J. Amer. med. Ass.*, 147, 1629.
Hughes, J. G., Jordan, R. G., and Hill, F. S. (1949). *Sth. med. J.*, 42, 296.
Silber, R. H., and Porter, C. C. (1954). *J. biol. Chem.*, 210, 923.
Ziff, M., Scull, E., Ford, D., McEwen, C., and Bunim, J. J. (1952). *A. M. A. Arch. intern. Med.*, 90, 774.

Emploi de l'injecteur à jet "Hypospray" pour l'administration intra-articulaire et locale d'acétate d'hydrocortisone

RÉSUMÉ

L'injecteur à jet "Hypospray" a été utilisé pour l'injection intra-articulaire. Sur la base de la récupération dans le liquide synovial du trypan bleu et de l'acétate d'hydrocortisone injectés, il apparut qu'une substantielle quantité du produit pénétrait la cavité articulaire. Des études radiologiques après l'injection de "Diodrast" révélèrent sa présence dans et autour de l'articulation.

Des injections furent faites à la fois avec un instrument standard et avec un injecteur à jet plus énergique. Avec ce dernier, 66% de 123 injections dans diverses articulations de malades atteints d'arthrite rhumatismale montrèrent une importante amélioration. Un petit groupe de malades atteint d'autres types d'arthrite et de rhumatisme non articulaire fut aussi traité avec de bons résultats. Les petites articulations des mains obtinrent le plus de bénéfice.

La technique de l'injection à l'"Hypospray" est simple et le procédé commode. Aucune complication sérieuse n'en a résulté.

Empleo del eyector "Hypospray" para la administración intra-articular y local de acetato de hidrocortisona

SUMARIO

El eyector "Hypospray" fué empleado para inyecciones intra-articulares. La recogida del líquido sinovial de tripan azul y de acetato de hidrocortisona inyectados permite estimar que una cantidad substancial del producto penetra la cavidad articular. Estudios radiológicos después de la inyección de "Diodrast" revelaron la presencia de éste dentro y alrededor de la articulación.

Se hicieron inyecciones con un instrumento ordinario y con un eyector más fuerte. Con el último, el 66% de 123 inyecciones en diferentes articulaciones de enfermos con artritis reumatoide reveló una mejoría importante. Se obtuvieron también buenos resultados en un pequeño grupo de enfermos afectos de otros tipos de artritis y de reumatismo extra-articular. Las pequeñas articulaciones de las manos beneficiaron más.

La inyección con "Hypospray" es técnicamente sencilla y el procedimiento es cómodo. No hubo complicaciones de importancia.

Ann. rheum. Dis. (1956), **15**, 233

THERAPEUTIC TRIALS IN ACUTE GOUTY ARTHRITIS

BY

MELVIN H. LEVIN, STANLEY MARCUS, DAVID STRANGE, AND ROBERT L. SWEZEY

From the Veterans Administration Center, Los Angeles, Calif., and the Department of Medicine, School of Medicine, University of California Medical Center, Los Angeles, California

(RECEIVED FOR PUBLICATION JULY 30, 1956)

Colchicine remains the agent of choice in the treatment of acute gouty arthritis. In recent years valuable additions to the therapeutic armamentarium in this disease include ACTH, cortisone, hydrocortisone acetate, prednisone, and Butazolidin (Wolfson, Hunt, Cohn, Robinson, and Duff, 1950; Gutman and Yü, 1950, 1952; Freyberg, 1955; Hartung, 1955; Steinbrocker, Neustadt, and Ehrlich, 1954). All of these are effective systemically, and in addition hydrocortisone acetate appears beneficial when administered intra-articularly.

The mechanism of action of colchicine (used either orally or intravenously) has been an enigma for centuries, and it was hoped that information on the *modus operandi* of these other potent anti-gout agents might shed some light upon it. Unfortunately, in spite of the mass of literature that has accumulated on the use of these drugs in the past 5 years, the mechanism by which they exert their effect has not been revealed. We are left then with the well-known non-specific "anti-phlogistic" explanation—a concept in need of further clarification.

An understanding of the mechanism by which therapeutic agents exert their effect represents a possible clue to the solution of the factors responsible for acute gouty arthritis. This is particularly true for the time-tested colchicine, since of all the drugs mentioned only colchicine is specific for the acute arthritis of gout alone.

Several hints relating to the possible effects of anti-gout agents have been suggested by recent work. One of these is the fact that colchicine given in therapeutic doses orally during studies of metabolic balance induces temporary Na, Cl, and H_2O retention (Levin, Rivo, and Bassett, 1953). This, coupled with the salt-retaining effects of ACTH, cortisone, hydrocortisone, and also Butazolidin, suggests that agents capable of inducing Na and Cl retention but devoid of an "anti-inflammatory" effect might profitably be explored in the treatment of acute gouty arthritis. For these reasons desoxycorticosterone was used in this study.

Another clue was the finding that certain steroids exert their "anti-phlogistic" effect when given locally (Hollander, 1953, 1955; Stevenson, Zuckner, and Freyberg, 1952). This suggested the possibility that colchicine exerted a purely local effect upon the inflammation of gouty arthritis. Before using colchicine locally, studies were done on rabbits (Levin, 1956). It was found that the colchicine solution commercially available for intravenous use, when administered intra-articularly into rabbit knee-joints in doses of 0·25 to 1·0 ml., produced no local synovial inflammatory response as determined by microscopic examination after 24 and 48 hours, isotonic saline being used as a control in the contralateral knee. It was, therefore, decided to use this agent intra-articularly in gouty joints.

The idea has often been put forward that acute gouty arthritis represents an allergic response of the articular and peri-articular structure to allergens so far unknown (Ferrannini and De Pergola, 1950; Violle, 1947; Harkavy, 1949). The rapidity of onset and the cardinal signs of inflammation plus the occasional history of what may represent ingestant allergy in certain gouty individuals suggest that an allergic reaction may be involved in this disease. The effect of steroids upon allergic ailments also seems to support this view. Accordingly, the effects of large doses of an anti-histamine, diphenhydramine hydrochloride*, were studied in this disease.

Finally, other drugs closely related to colchicine structurally were studied from the point of view that certain differences in chemical composition may produce differences in physiological and pharmacological response. Colcemide (Demecolcine†), a

* Benadryl, Parke-Davis.

† "Demecolcine" was generously supplied by Ciba Pharmaceutical Products, Inc.

new alkaloid obtained from the bulbs of *Colchicum autumnale*, differs from colchicine only in that the acetyl group of the latter is replaced by a methyl group. Since this agent has been used rather extensively on patients with tumours and lymphomata and is relatively safe in small doses (Moeschlin, Meyer, and Lichtmen, 1953; Leonard and Wilkinson, 1955; Bock and Gross, 1953), it was decided to test it in gouty patients. Complete blood counts were performed on this group of gouty subjects at least twice weekly.

Material and Methods

As a result of the above speculations, four therapeutic programmes were established.

(1) Desoxycorticosterone intramuscularly;
(2) An intravenous solution of colchicine intra-articularly;
(3) Benadryl intravenously and orally;
(4) Colcemide ("Demecolcine") intravenously and orally.

All the patients so treated were individuals with known gout established by the usual clinical, laboratory, and *x*-ray criteria. Only patients who had previously responded to full oral doses of colchicine were used and the response of all agents was compared with that of previous courses of colchicine. Particulars of the dosage, route of administration, site of attack, response, and side-effects are given in the Table (opposite).

Results

DOCA.—None of the three gouty episodes treated with DOCA responded well. Patient 1, though responding moderately well subjectively, demonstrated slow resolution of the inflammatory process; comparing this to the natural course of his attacks, he felt that the resolution of the attack was accelerated. In no other patient was there any evidence that DOCA altered the illness either favourably or unfavourably.

Local Colchicine.—In all four patients treated with the intravenous solution of colchicine intra-articularly, the disease progressed during treatment. In no instance was there any favourable influence upon the gouty attack and other agents were required to terminate the episode. Three of the four, particularly Patient 4, seemed to become definitely worse; within several hours after the injection rapid exacerbation of the inflammatory process out of proportion to the usual progress of the attack was observed. All responded well to other agents and no instance of residual joint damage was noted.

Benadryl.—None of the three cases receiving Benadryl showed any improvement. No evidence of undesirable side-effects was seen.

Colcemide.—All of the five patients treated with colcemide ("Demecolcine") showed clinical improvement within 48 hours, the response being comparable to that expected with therapeutic doses of colchicine. In Patients 12 and 15 the initial response was followed by a re-exacerbation of the process about 2 days after therapy was begun.

Side-effects were not observed, though in Patient 15 diarrhoea, which had been induced by colchicine, continued throughout the period of colcemide treatment.

Discussion

It is obvious that our experience with the use of DOCA, local colchicine, and Benadryl in acute gouty arthritis, was unrewarding. No evidence was found of any ameliorating effect upon the disease, in the dosage and methods used. Local colchicine appeared to aggravate the severity of the attack. Since this material was innocuous in rabbits, the inference is that species differences, changes inherent in gouty patients, or other unknown factors were responsible for this phenomenon. The evidence would favour the idea that the mechanism of action of colchicine is not a local one.

In addition, although this is certainly not conclusive, the failure of Benadryl to affect the disease seems to show that allergy *per se*, in the usual clinical sense with histamine release, does not play a central role in acute gouty arthritis.

The failure of DOCA to help these patients, who later responded to other known anti-gout agents, most of which are salt-retaining, suggests that sodium and chloride retention *per se* is not a crucial factor in the *modus operandi* of the specific anti-gout effect of colchicine and other agents.

The results of the use of colcemide (Demecolcine) are interesting, in that this compound appears to exert a definite therapeutic effect in acute gouty arthritis. This effect was usually good and occasionally dramatic, but seemed to have no obvious advantage over colchicine. The dose used was 1 mg. for seven doses, and it is possible that higher doses would produce better results.

Worthy of emphasis was the lack of significant gastro-intestinal side-effects with colcemide. Similarly, the doses used caused no anaemia, thrombocytopenia, or leucopenia.

Since this work was begun a paper has appeared by Kuzell, Schaffarzick, and Naugler (1955), on the effect of intravenous colcemide in acute gout.

TABLE

Patient No.	Drug	Dose and Frequency	Route	No. of Doses	Site of Gouty Attack	Therapeutic Response	Side-Effects
1	DOCA	10 mg. 12-hrly	Intramuscular	Seven	L. wrist	In 48 min. pain better, objectively little change. In 96 min. pain gone; incomplete resolution objectively.	None
2		10 mg. 12-hrly	Intramuscular	Six	R. metatarsophalangeal	Poor. Progression during therapy	Vomited once Demerol effect
3		10 mg.	Intramuscular	One	L. ankle	No effect	None
4	Colchicine (intravenous solution)	1 mg.	Intra-articular	One	L. ankle	Poor. Progression after injection	None
5		1 mg.	Intra-articular	One	L. knee	Poor. Progression after injection	None
6		1 mg.	Intra-articular	One	R. knee	Poor. Progression after injection	None
7		1 mg. 24-hrly	Intra-articular	Two	L. knee	Poor. Attack progressed, but later responded to oral colchicine	None
8	Benadryl	50 mg.	Intravenous	One	R. knee	No effect, then marked improvement on ACTH	None
		4-hrly	Oral	Ten			
9		50 mg.	Intravenous	One	R. ankle	Poor. No response, then usual response with colchicine	None
		4-hrly	Oral	Ten			
10		50 mg.	Intravenous	One	R. ankle	Poor. No response, then usual response with colchicine	None
11	Colcemide (Demecolcine)	2 mg. daily	Intravenous	Two	R. elbow	Improvement definite, but not dramatic In 48 hrs pain better In 72 hrs tenderness markedly improved	None
		3 mg. daily	Oral	One			
12		1 mg. 2-hrly	Oral	Seven	R. first metatarsophalangeal R. first tarsal	Marked relief in 3 hrs Rebound in 48 hrs Marked relief 24 hrs later	None
13		1 mg. 2-hrly	Oral	Seven	Both knees and tarsals	Excellent response in 24 hrs	None
14		1 mg. 2-hrly	Oral	Seven	R. ankle and R. first metatarsophalangeal	Slight improvement in 24 hrs Gradual resolution in 7 days after colchicine	None
15		1 mg. 2-hrly	Oral	Seven	L. metatarsophalangeal and dorsum L. foot and ankle R. metatarsal and knee	Good improvement in 48 hrs with minimal residual symptoms Mild flare-up, improving in 24 hrs	Colchicine-induced diarrhoea before colcemide

Using doses of 1 to 4 mg., usually in two successive daily intravenous injections, these workers found that fifteen out of twenty patients "enjoyed complete remission within 48 hours" of treatment. Our data supports these findings and suggests that oral as well as intravenous therapy is effective.

This drug, in the doses used, seems to be relatively safe and fairly effective in gouty arthritis, but we feel that a much larger experience with it is necessary before it can be recommended in gout.

Summary

(1) The results of therapeutic trials of four drugs in fifteen patients with acute gouty arthritis is discussed.

(2) DOCA (intramuscular) and Benadryl (intravenous) seemed to be ineffective in acute gouty arthritis.

(3) An intravenous solution of colchicine injected intra-articularly in 1 mg. doses was ineffective in terminating acute attacks of gouty arthritis.

(4) Colcemide (Demecolcine), a new compound structurally related to colchicine, gave good results when used orally in 1-mg. doses as a therapeutic agent in gouty arthritis.

REFERENCES

Bock, H. E., and Gross, R. (1953). *Klin. Wschr.*, **31**, 816.
Ferrannini, A., and De Pergola, E. (1950). *Rif. Med.*, **64**, 1241.
Freyberg, R. H. (1955). "Meticorten and Meticortelone". The First International Conference on their Clinical and Metabolic Effects, May 31—June 1, 1955, New York. Published by the Schering Corporation.
Gutman, A. B., and Yü, T. F. (1950). *Amer. J. Med.*, **9**, 24.
——, —— (1952). *Ibid.*, **13**, 744.
Harkavy, J. (1949). *J. Amer. med. Ass.*, **139**, 75.
Hartung, E. F. (1955). "Meticorten and Meticortelone." The First International Conference on their Clinical and Metabolic Effects, May 31—June 1, 1955, New York. Published by the Schering Corporation.
Hollander, J. L. (1953). *Ann. intern. Med.*, **39**, 735.
—— (1955). "Meticorten and Meticortelone". The First International Conference.
Kuzell, W. C., Schaffarzick, R. W., and Naugler, W. E. (1955). *Arch. intern. Med.*, **96**, 153.
Leonard, B. J., and Wilkinson, J. F. (1955). *Brit. med. J.*, **1**, 874.
Levin, M. H. (1956). Unpublished data.
——, Rivo, J. B., and Bassett, S. H. (1953). *Amer. J. Med.*, **15**, 525.
Moeschlin, S., Meyer, H., and Lichtmen, A. (1953). *Schweiz. med. Wschr.*, **83**, 990.
Steinbrocker, O., Neustadt, D. H., and Ehrlich, M. (1954). *Med. clin. N. Amer.*, **38**, 611.
Stevenson, C. R., Zuckner, J., and Freyberg, R. H. (1952). *Annals of the Rheumatic Diseases*, **11**, 112.
Violle, P. L. (1947). *Presse méd.*, **55**, 882.
Wolfson, W. Q., Hunt, H. D., Cohn, C., Robinson, W. D., and Duff, I. F. (1950). *J. Mich. med. Soc.*, **49**, 1058.

Essais thérapeutiques dans l'arthrite goutteuse aiguë

RÉSUMÉ

(1) Les résultats d'essais thérapeutiques de quatre produits sur quinze malades atteints d'arthrite goutteuse aiguë sont discutés.

(2) DOCA (intramusculaire) et "Benadryl" (intraveineux) semblèrent ineffectifs.

(3) Une solution intraveineuse de colchicine injectée intra-articulairement en doses de 1 mg. fut impuissante à arrêter les attaques aiguës.

(4) Colcémide (Demecolcine), un composé nouveau, structuralement apparenté à la colchicine, administré par voie buccale en doses de 1 mg., donna de bons résultats thérapeutiques.

Ensayos terapéuticos en la artritis gotosa aguda

SUMARIO

(1) Se discuten los resultados de ensayos terapéuticos de cuatro productos sobre quince enfermos afectos de artritis gotosa aguda.

(2) DOCA (intramuscular) y "Benadryl" (intravenoso) no parecieron eficaces.

(3) No se consiguió terminar ataques agudos con una solución endovenosa de colchicina administrada intra-articularmente en dosis de 1 mg.

(4) Colcemide (Demecolcine), un compuesto nuevo, estructuralmente relacionado con la colchicina, administrado por vía oral en dosis de 1 mg., dió buenos resultados terapéuticos.

Ann. rheum. Dis. (1956), **15**, 237.

CLINICAL AND METABOLIC EFFECTS OF Δ^1-DEHYDRO-9-ALPHA-FLUORO HYDROCORTISONE ACETATE

BY

L. VILLA, G. SALA, AND C. B. BALLABIO

Clinica Medica dell'Università di Milano, Centro Reumatologico

(RECEIVED FOR PUBLICATION MAY 1, 1956)

The discovery of the therapeutic properties of certain steroids has recently given rise to interesting chemical and pharmacological problems. The remarkable antiphlogistic activities of halogenated derivatives of hydrocortisone, and the disappearance of secondary effects obtained by the Δ^1-diene derivatives of cortisone, have suggested the synthesis of a steroid which joins the two chemical characteristics (Hirschmann, Miller, Beyler, Sarett, and Tishler, 1955; Stafford, Barnes, Bowman, and Meinzinger, 1955; Fried, Florey, Sabo, Herz, Restivo, Borman, and Singer, 1955; Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, 1955).

Preliminary experiments have been carried out with the following derivative: Δ^1-dehydro-9-α-fluoro hydrocortisone acetate, the structural formula of which is shown in Fig. 1.

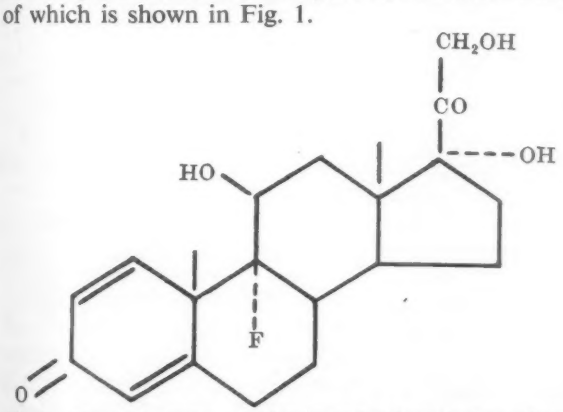


Fig. 1.—Chemical structure of Δ^1-dehydro-9-α-fluoro hydrocortisone acetate.

The first biological researches show that in the liver glycogen deposition test the new steroid is 25 to 50 times as potent as hydrocortisone acetate; in the reduction of sodium excretion in the adrenalectomized rat it is two to five times stronger than desoxycorticosterone acetate (DCA).

In the clinical field the work of Thorn, Renold, Morse, Goldfien, and Reddy (1955) makes evident that, in one normal subject and in three patients suffering from Addison's disease, Δ^1-9-α-fluoro hydrocortisone acetate has 50 and 20 times more effect than hydrocortisone on electrolyte and organic metabolism respectively.

Methods

The new steroid was tested in three subjects with rheumatoid arthritis, in one with chronic gout, and in two with Addison's disease. Daily 4- to 10-mg. doses were administered orally for 10 days in the rheumatic diseases and 0·5 to 1 mg. for 7 days in Addison's disease.

The therapeutic properties of Δ^1-dehydro-9-α-fluoro hydrocortisone acetate (Δ^1-9-α-FFa) were estimated qualitatively and quantitatively, with particular reference to the comparison of activity with cortisone acetate (Ea), prednisolone (Δ^1 F), and 9-α-fluoro hydrocortisone acetate (9-α-FFa).

The metabolic study was carried out according to the methods described in previous papers (Villa, Ballabio, and Sala, 1955; Sala, D'Amico, Pasargiklian, Amira, and Ballabio, 1955) using the tests set out in the Table.

TABLE
LABORATORY TESTS

Investigation	Authors	Date
Sedimentation rate	Westergren	1924
Serum mucoproteins	Winzler, Devor, Mehl, and Smyth	1948
Plasma and urinary Na and K (by flame photometry)	Mosher, Boyle, Bird, Jacobson, Batchelor, Iseri, and Myers	1949
Plasma chloride	Van Slyke and Hiller	1947
Urinary chloride	Harvey	1910
Serum carbon dioxide	Van Slyke and Cullen	1917
Plasma and urinary endogenous creatinine	Bonsnes and Taussky	1945
Blood glucose	Hagedorn and Jensen	1923
Blood pyruvic acid	Friedemann, Haugen, and Kmieciak	1945
Plasma cholesterol	Bloor	1916

Results

Antirheumatic Activity.—Three patients affected by rheumatoid arthritis showed marked subjective and objective improvement within the first 48 hrs

of treatment, with relief of pain and aching on motion, reduction of stiffness and swelling, and lessening of tenderness, the improvement in function being clearly evident. The subject suffering from gout showed a subjective and objective improvement; the local improvement was accompanied with a general one, with a corresponding euphoria.

Two cases presented sleeplessness and restlessness.

Relapses occurred on discontinuing treatment in all the cases observed up to the present.

A definite decrease was observed in the sedimentation rate and in serum mucoproteins.

$\triangle^1$-9-α-fluoro hydrocortisone acetate possesses all the anti-inflammatory and antirheumatic properties of cortisone and prednisone.

Comparing it with other steroids, maintenance therapy produces similar effects with doses two or three times lower than those required with prednisolone and practically equivalent to those required with 9-α-fluoro hydrocortisone acetate, so that its antirheumatic activity may be considered ten–fifteen times higher than that of cortisone acetate.

Metabolic Activity

Salt and Water Balance.—A marked difference between the effects of prednisolone and $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate was observed at doses clinically equivalent.

In fact prednisolone (or prednisone) increases urine volume and sodium excretion without greatly affecting potassium loss; serum electrolytes not being consistently modified. On the contrary $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate causes initial decrease of urine volume, strong sodium retention, and potassium loss*; successively, after 3 to 4 days of treatment, a diuresis occurs with sodium and chloride loss up to values higher than the basal ones (Fig. 2).

It is worth mention that a similar pattern in the sodium balance was observed in the same cases, treated with equivalent doses of 9-α-fluoro hydrocortisone acetate.

In the serum a sharp fall in potassium to 2·5 to 2 mEq/l., and a slight increase in sodium concentration are observed; haematocrit values (per cent. cells) are constantly decreased, as an expression of hemodilution (Fig. 3).

The marked activity of $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate on water and electrolyte metabolism causes an increase in body weight, blood pressure, and heart size, to a decrease of heart rate, and alterations in the electrocardiogram (lengthening of QT-space, displacing of ST-segment, depression of T-wave).

In adrenal insufficiency, daily doses of 0·5 to 1 mg. $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate are able to normalize electrolyte metabolism or even to cause sodium retention and potassium loss.

In these preliminary experiments we have not

* In one case the total sodium daily urinary excretion fell from 172 to 5 mEq. (Fig. 2).

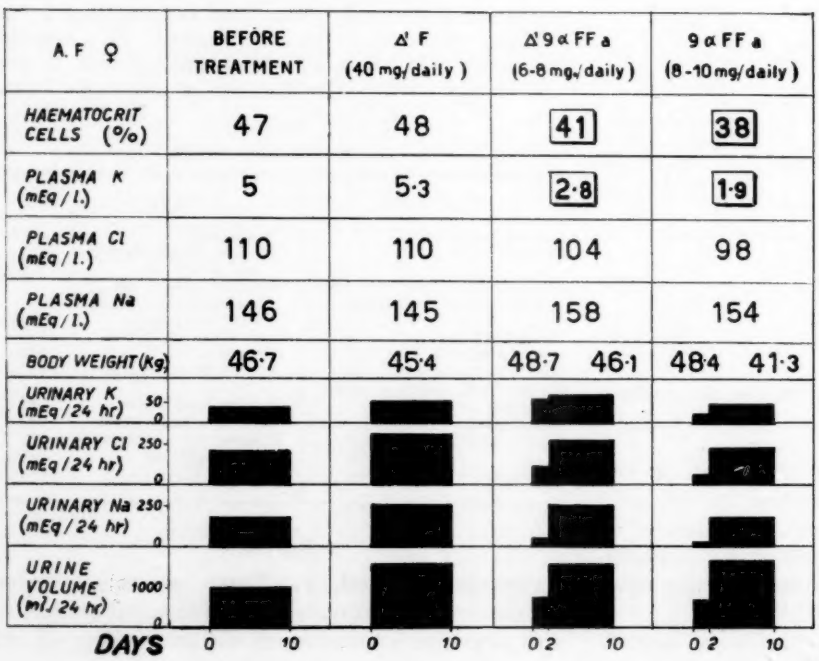


Fig. 2.—Metabolic balance in a woman aged 43 with rheumatoid arthritis treated with various steroids.

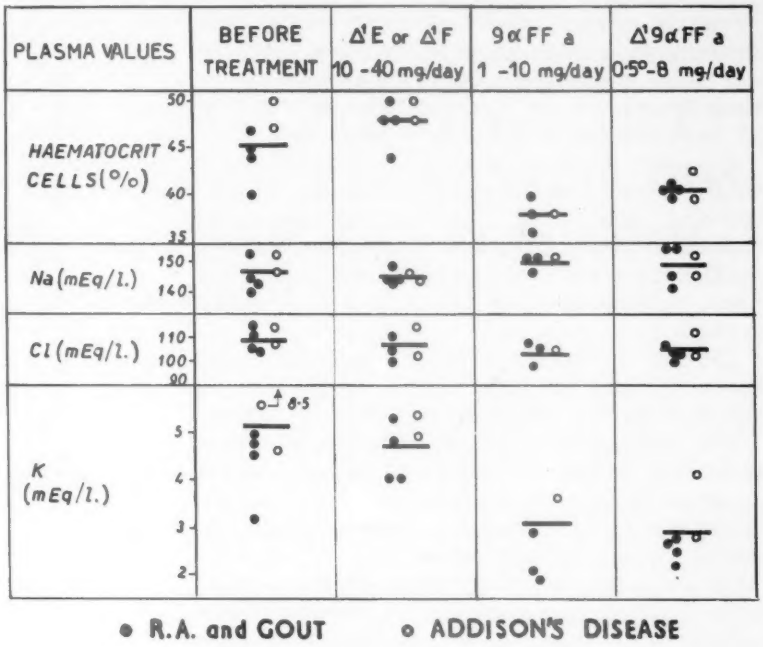


Fig. 3.—Effect of various steroids on plasma electrolytes in three patients with rheumatoid arthritis, one with gout, and two with Addison's disease.

gone below a daily 500 γ dose, but the intensity of the obtained effect suggests the use of reduced doses (100–200 γ).

In plasma a loss of potassium and a moderate increase in sodium and CO_2 may occur, while the chlorides remain almost unchanged (Fig. 3).

A fall in the ratio Na/K (from 0·41 to 0·24) in the non-stimulated saliva was noticed in one case after a 3-days treatment with 500 γ of the new steroid, administered daily.

As far as the diuretic activity of corticoids is concerned, $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate is even more efficient than prednisolone in increasing the urine output after a water load in Addison's disease, at doses 10–20 times smaller.

Carbohydrate Metabolism.—In three out of the four rheumatic patients treated up to date, who presented a normal glucose tolerance test before the treatment, $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate did not modify glucose tolerance and did not cause glycosuria.

It is to be noticed that a decrease in glucose tolerance had previously been caused in two out of these cases by treatment with prednisolone (30–40 mg. administered daily).

In one patient, a woman aged 43, 8-mg. doses of the new steroid daily for 10 days caused diabetes with fasting blood glucose of 160 mg. per cent., pyruvic acid of 2·45 mg. per cent., daily glycosuria of 15–20 g., and a decrease in glucose tolerance (Fig. 4). It must be noted that this patient showed a slight decrease in carbohydrate tolerance before treatment.

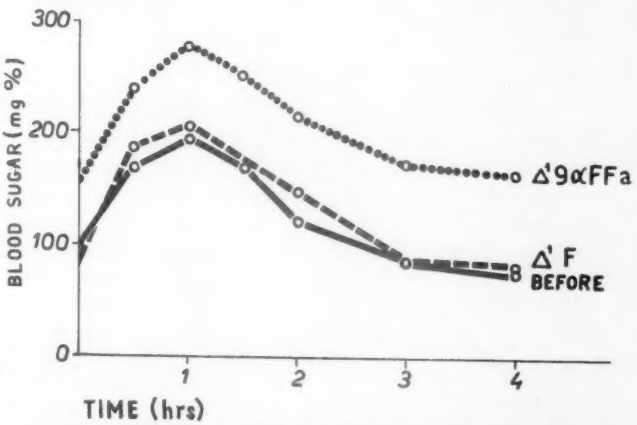


Fig. 4.—Influence of $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate ($\triangle^1$-9-α-FFa) and of prednisolone ($\triangle^1$F) on results of oral glucose tolerance tests in a woman aged 43 (0·75 g. glucose per kg.).

Comment

Practical considerations prevented us from studying a large series of patients, but our results allow us to define the clinical and metabolic activity of $\triangle^1$-dehydro-9-α-fluoro hydrocortisone acetate.

From the clinical point of view this steroid shows a strong antirheumatic action when administered in

doses remarkably inferior to those needed with cortisone and prednisone or prednisolone. According to our experiments, the new steroid is two to three times more active than prednisone and 10 to 25 times more active than cortisone acetate.

However, the introduction of a double bond in C_1–C_2 is not able to avoid the strong mineralcorticoid activity of 9-α-fluoro hydrocortisone acetate, so that the high activity against electrolyte metabolism prevents the practical use of Δ^1-9-α-fluoro hydrocortisone acetate, at least in rheumatic diseases.

Sodium retention, although temporary and reversible, may be dangerous in the presence of abnormal cardiocirculatory conditions.

The constant and lasting decrease of plasma potassium causes a depletion in intracellular potassium and may cause serious functional changes in the nervous and circulatory systems, as demonstrated by the electrocardiogram.

On the other hand, the high mineralcorticoid activity of Δ^1-dehydro-9-α-fluoro hydrocortisone suggests that it should be used in Addison's disease to normalize the metabolism; efficient doses of this new steroid in Addison's disease seem about the same size as with aldosterone.

Δ^1-9-α-fluoro hydrocortisone acetate appeared to have a diabetogenic effect, but the small number of patients treated prevents us from establishing the importance of this side-effect as compared with cortisone, prednisone, and prednisolone.

Summary

(1) The clinical and metabolic effects of Δ^1-dehydro-9-α-fluoro hydrocortisone acetate were determined in four patients affected by rheumatic diseases, and in two patients with adrenal insufficiency.

(2) In rheumatic disease the compound is two to three times more potent than prednisone, and 10–25 times more active than cortisone acetate. In Addison's disease daily doses of 0·5 to 1 mg. are able to reduce most of the metabolic alterations to normal.

(3) The marked effect on electrolyte metabolism (sodium retention and potassium loss) prevents the practical use of this drug in rheumatic diseases; but it may be usefully employed to treat adrenal insufficiency.

The authors wish to thank Merck and Co., Rahway, N.J., for the Δ^1-dehydro-9-α-fluoro hydrocortisone acetate, the 9-α-fluoro hydrocortisone acetate, and the prednisolone used in this study.

REFERENCES

Bloor, W. R. (1916). *J. biol. Chem.*, **24**, 227.
Bonsnes, R. W., and Taussky, H. H. (1945). *Ibid.*, **158**, 581.
Fried, J., Florey, K., Sabo, E. F., Herz, J. E., Restivo, A. R., Borman, A., and Singer, F. M. (1955). *J. Amer. chem. Soc.*, 77, 4181.
Friedemann, T. E., Haugen, G. E., and Kmieciak, T. C. (1945). *J. biol. Chem.*, **157**, 673.
Hagedorn, H. C., and Jensen, B. N. (1923). *Biochem. Z.*, 135, 46.
Harvey, S. C. (1910). *Arch. intern. Med.*, **6**, 12.
Hirschmann, R. F., Miller, R., Beyler, R. E., Sarett, L. H., and Tishler, M. (1955). *J. Amer. chem. Soc.*, 77, 3166.
Hogg, J. A., Lincoln, F. H., Nathan, A. H., Hanze, A. R., Schneider, W. F., Beal, P. F., and Korman, J. (1955). *Ibid.*, 77, 4438.
Mosher, R. E., Boyle, A. J., Bird, E. J., Jacobson, S. D., Batchelor, T. M., Iseri, L. T., and Myers, G. B. (1949). *Amer. J. clin. Path.*, **19**, 461.
Sala, G., D'Amico, G., Pasargiklian, E., Amira, A., and Ballabio, C. B. (1955). *Reumatismo*, 7, 127.
Stafford, R. O., Barnes, L. E., Bowman, B. J., and Meinzinger, M. M. (1955). *Proc. Soc. exp. Biol. (N.Y.)*, **89**, 371.
Thorn, G. W., Renold, A. E., Morse, W. I., Goldfien, A., and Reddy, W. J. (1955). *Ann. intern. Med.*, **43**, 979.
Van Slyke, D. D., and Cullen, G. E. (1917). *J. biol. Chem.*, 30, 289.
——, and Hiller, A. (1947). *Ibid.*, **167**, 107.
Villa, L., Ballabio, C. B., and Sala, G. (1955). *Annals of the Rheumatic Diseases*, **14**, 251.
Westergren, A. (1924). *Ergebn. inn. Med. Kinderheilk.*, **26**, 577.
Winzler, R. J., Devor, A. W., Mehl, J. W., and Smyth, I. M. (1948). *J. clin. Invest.*, **27**, 609.

Effets cliniques et métaboliques de l'acétate de Δ^1-dehydro-9-α-fluoro hydrocortisone

RÉSUMÉ

(1) Les effets cliniques et métaboliques de l'acétate de Δ^1-dehydro-9-α-fluoro-hydrocortisone furent déterminés chez quatre sujets atteints de maladie rhumatismale et chez deux sujets atteints d'insuffisance surrénale.

(2) Pour les cas de rhumatisme, le produit est deux ou trois fois plus puissant que la prednisone et 10 à 25 fois plus actif que l'acétate de cortisone. Dans la maladie d'Addison des doses quotidiennes de 0,5 à 1 mg. sont capables de ramener la plupart des altérations métaboliques à la normale.

(3) L'effet marqué sur le métabolisme électrolyte (rétention du sodium et perte du potassium) empêche l'utilisation pratique de ce médicament dans les maladies rhumatismales, mais il peut être utilement employé pour traiter l'insuffisance surrénale.

Efectos clínicos y metabólicos del acetato de Δ^1-dehidro-9-α-fluoro hidrocortisona

SUMARIO

(1) Se determinaron los efectos clínicos y metabólicos del acetato de Δ^1-dehidro-9-α-fluoro hidrocortisona en cuatro enfermos afectos de enfermedades reumáticas y en dos con insuficiencia suprarrenal.

(2) En la enfermedad reumática este compuesto es dos o tres veces más poderoso que prednisone y 10 a 25 veces más activo que el acetato de cortisona. En la enfermedad de Addison dosis diarias de 0,5 a 1 mg. pueden normalizar la mayoría de las alteraciones metabólicas.

(3) El efecto marcado sobre el metabolismo electrolítico (retención de sodio y perdida de potasio) previene el uso práctico de este medicamento en las enfermedades reumáticas; se puede, sin embargo, emplearle útilmente para tratar insuficiencia suprarrenal.

Ann. rheum. Dis. (1956), **15**, 241.

CHANGES IN THE INTRA-ARTICULAR TEMPERATURE OF THE KNEE WITH CUTANEOUS VASOCONSTRICTION AND VASODILATATION OF THE TOES IN NORMAL SUBJECTS*

BY

RAYMOND PENNEYS AND NATHAN M. SMUKLER

From the Vascular Section of the Robinette Foundation and the Arthritis Section, Department of Medicine, Hospital of the University of Pennsylvania

(RECEIVED FOR PUBLICATION JULY 10, 1956)

Hollander and Horvath (1949) and Horvath and Hollander (1949) have reported two sets of experiments in which they studied the changes induced in the intra-articular temperature by the application of cold, or heat, to another part of the body. In the first series of experiments, the application of cold packs to one knee caused an increase in the temperature of the other knee joint, and hot packs to one knee caused a decrease in the temperature of the other knee joint. In the second series of experiments, the immersion of one leg in water at 103° F. did not alter the temperature of the ankle joint of the opposite leg even though it produced cutaneous vasodilatation of the toes of the unimmersed foot.

Stimulated by their work, we became interested in measuring the effect of cold and heat, somewhat differently applied, upon joint temperature. Body cooling has been known for many years to elicit marked cutaneous vasoconstriction in the extremities, just as body warming has been known to elicit marked cutaneous vasodilatation in the extremities. For certain physiological and clinical considerations to be discussed later, we are describing in this paper the changes in joint temperature which accompany these conspicuous changes in skin blood flow.

Method

The seven subjects studied were healthy young adults, 20 to 35 years of age (average 27). Skin surface temperatures were measured by thermocouples attached by one layer of adhesive tape to the skin on the dorsal surface of the toes of both feet, and to the skin of the anterior surface of each knee. The knee joint was chosen for measurement of the intra-articular temperature because its size facilitates the insertion of the thermocouple within the joint space. Intra-articular temperatures were obtained by the technique of Horvath and Hollander (1949); using a medial approach, a 19 needle, bored to an 18 internal diameter, was inserted into the joint space. A fine copper-constantan thermocouple was threaded through the needle for a distance greater than the length of the needle, to insure the projection of its tip into the joint space. The needle and all thermocouples were left *in situ* throughout the entire experiment. The intra-articular temperature was measured in only one extremity, while the skin temperatures were taken in both extremities in order to determine whether the presence of the needle, and thermocouple, within the joint space in some manner influenced the skin temperature of that extremity. No difference between the skin temperatures of the two extremities was found. The skin and intra-articular temperatures were recorded every 2 minutes by a Brown potentiometer. Oral temperatures were also obtained, from time to time, with a standard clinical mercury thermometer.

Observations were made first during a state of cutaneous vasoconstriction of the toes, and then during a state of cutaneous vasodilatation. Cutaneous vasoconstriction was induced by exposure of the fasting subject, clad only in a light cotton dressing-gown and underwear shorts, to cool air in a thermoregulated, constant-temperature, cool room with air temperature usually of 21° C. Skin temperature of the toes of 24° C., or less, was used as the indication of a state of vasoconstriction. Cutaneous vasodilatation was induced by warming the body and by giving food to the subject. Body-warming was accomplished by placing heating pads over the chest and abdomen and covering the subjects with blankets so that only the face, knees,

* This work was supported in part by a grant (G-51-30) from the Life Insurance Medical Research Fund, and a grant from the Helen Augusta Parkhill Memorial Fund.

TABLE

INTRA-ARTICULAR AND SKIN TEMPERATURES WITH BODY-COOLING AND BODY-WARMING

Experiment No.	Room Temperature (° C.)		Oral Temperature (° C.)		Skin Temperature† (° C.)				Intra-Articular Temperature† (° C.)	
					Knee		Toes‡			
	C	W	C	W	C	W	C	W	C	W
1	22·0	21·4	36·8	37·2	27·6	35·2	21·5	20·9	32·2	37·8*
2	21·2	21·2	36·7	36·3	27·2	27·6	21·9	32·2	32·4	31·2
3	21·4	21·4	36·7	37·0	28·0	35·6	21·9	33·5	32·0	37·0
4	21·0	20·6	—	—	26·2	27·8	22·5	32·6	33·2	35·6
5	20·8	20·8	36·7	37·0	26·8	34·4	21·5	32·5	32·0	38·4*
6	21·2	21·4	36·9	37·0	27·0	27·0	21·3	33·8	31·0	30·6
7	25·1	25·1	37·0	36·9	30·2	36·2	24·0	32·5	31·6	38·0*
Average ..					27·6		22·1		32·1	

C = While exposed to cool air. W = During body-warming.
† Skin and intra-articular temperatures were taken in the same extremity and the same steady state.
‡ Average of at least three toes.

* These three values of the joint temperature bear comment since they are higher than the corresponding oral temperatures, and the intra-articular temperature of inflamed, arthritic joints (Hollander, Stoner, Brown, and DeMoor, 1951). The explanation is probably as follows: Oral temperatures, taken only incidentally in our experiments as a convenient approximation of the "body temperature", are usually less than the rectal temperature (Bard, 1941), and the rectal temperature can be less than the temperature of other parts of the body, including the arterial blood of an extremity (Bazett, Love, Newton, Eisenberg, Day, and Forster, 1948). The arterial blood coming to the knee joint, in our experiments, was probably still quite warm as blankets covered most of the thigh so that the blood had to travel only a few inches through that portion of the thigh exposed to cool air. The validity of these three high joint temperatures is, in a sense, confirmed by the high skin temperatures (34·4, 35·2, and 36·2° C.) obtained in these three experiments, since the deep tissues of an extremity, when surrounded by cool air, must have a temperature higher than that of the skin (Bazett, Love, Newton, Eisenberg, Day, and Forster, 1948).

One very likely explanation for these three joint temperatures being higher than those of arthritic joints is that the arthritic patients were in a cool room and not body warmed. Our high joint temperatures were obtained only with body warming.

and feet were exposed to the air. Subjects were considered to be in a state of cutaneous vasodilatation when the skin temperature of the toes rose to 30° C. or higher. In one subject (Experiment 1, Table, Figure, opposite), we were unable to induce vasodilatation of the toes despite prolonged body-heating.

All results are reported for periods when the skin and joint temperatures were stable, toward the end of the period of body-cooling or toward the end of the period of body-warming. Body-cooling averaged about 45 minutes, body-warming about 2 hours.

Results

(1) With body-cooling, when the toes were in a state of cutaneous vasoconstriction, the intra-articular temperatures were within the narrow range of 31° to 33·2° C.

(2) With body-warming, when the toes were in a state of cutaneous vasodilatation, the joint temperature increased in four experiments (Nos 3, 4, 5, and 7) to an average of 37·3° C. but did not increase in two experiments (2 and 6). In a single instance (Experiment 1) the toes remained in a state of cutaneous vasoconstriction while the joint temperature increased to 37·8° C. Thus, in only four of seven experiments did both the intra-articular temperature and the cutaneous temperature of the toes increase in response to body-warming.

(3) With body-warming, the intra-articular changes were much better correlated with the temperature changes of the skin of the knee. Whenever the joint temperature increased with body-warming (Experiments 1, 3, 4, 5, and 7), the skin temperature of the knee also increased, and whenever the joint temperature failed to increase with body-warming, the skin temperature also remained unchanged (Experiments 2 and 6).

Discussion

These experiments show that with body-cooling and body-warming no fixed relationship exists between the temperature of the knee joint and the temperature of the skin of the toes in the same extremity. The intra-articular temperature of the knees of seven normal subjects varied over the wide range of 31 to 38° C., with either cutaneous vasoconstriction or vasodilatation in the toes. On the other hand, there is a definite relationship between the intra-articular temperature and the temperature

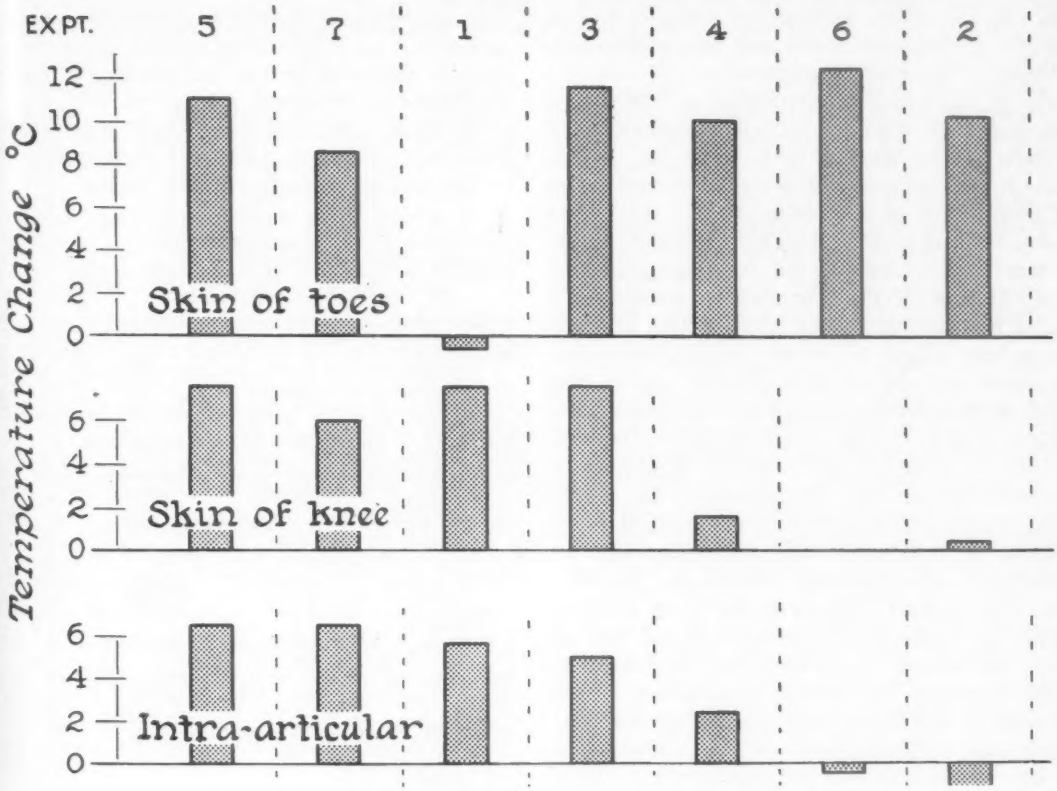


Fig. 1.—Changes in intra-articular and skin temperatures with body-warming.

of the skin directly over the joint. If the temperature of the skin over the joint was lowered to approximately 27° C. by body-cooling, the joint temperature to between 31 and 33·2° C.; if the skin temperature over the joint was raised to approximately 35° C. by body-warming, the joint temperature rose to between 37 and 38·4° C. Thus, the cutaneous temperature of the knee appears to be a reliable index of the intra-articular temperature of the knee joint, in these conditions.

Body-cooling and body-warming affect the temperature of the knee joint differently from the cold packs and hot packs used by Horvath and Hollander (1949). Although our experiments resemble theirs, in that the temperature changes in the knee joint were produced by the application of cold and heat elsewhere to the body, they differ in several important features: the cold and warmth in our experiments were considerably less intense, and were applied to much larger areas and for much longer periods of time. For these and perhaps other reasons the mechanism responsible for changes in joint temperature in our studies is probably different from that responsible for the joint temperature changes noted by Horvath and Hollander. The mechanism in our experiments may well be the same as that producing the skin temperature changes resulting from body-cooling and body-warming. Such skin temperature changes, especially those resulting from body-warming, have been the subject of many investigations (Gibbon and Landis, 1932; Bazett, 1949; Montgomery, Naide, and Freeman, 1941; Richards, 1946; Landis and Gibbon, 1933; Pickering, 1932; McKerslake and Cooper, 1954; Abramson, 1944; DuBois, 1948). Some workers have shown that a considerable time is required after heat is applied before the skin temperature starts to increase, and also that this increase can be prevented by trapping the warmed blood in the area being directly heated. They concluded therefore that such an increase in skin temperature depends largely upon the warming of blood and the arrival of this warmed blood at a "central" terminus (Pickering, 1932; DuBois, 1948; Fulton, 1949; Selle, 1952). The changes in joint temperature resulting from the use of cold and hot packs, on the other hand, came on very quickly after the application of the packs and are attributed

entirely to a reflex mechanism (Horvath and Hollander, 1949), presumably not depending upon any change in the blood temperature.

If the changes in joint temperature with body-cooling and body-warming in our experiments are due to changes in blood flow to the joint, just as changes in skin temperature are due to changes in blood flow to the skin (Montgomery, Naide, and Freeman, 1941; Richards, 1946), then our observations may have some clinical implications. The relatively low values in joint temperature regularly produced by exposure to cool air would indicate relatively low values of blood flow to the joint, which might account, in part, for the report that exposure to environmental cold and dampness may aggravate certain rheumatic conditions (Holbrook, 1953). The relatively high values of the joint temperature which can be produced by body-warming would indicate that body-warming is of therapeutic value if, and when, rapid blood flow to the joint is advantageous. Although Bonney, Hughes, and Janus (1952) have shown by plethysmography that body-heating increases blood flow to the knee segment, it is realized that factors other than blood flow to the joint (*e.g.* a change in the temperature of the blood as it courses through the extremity (see footnote to Table), or a change in blood flow to the skin and soft tissues surrounding the joint) may also have brought about some of the changes in joint temperature observed in our experiments.

Summary

(1) The intra-articular temperature of the knee of seven normal subjects was measured during a state of cutaneous vasoconstriction of the toes, induced by body-cooling; and then during a state of cutaneous vasodilatation of the toes, induced by body-warming. With cutaneous vasoconstriction from body-cooling, the intra-articular temperature remained within a narrow range (31 to 33·2° C.), but with vasodilatation the joint temperature varied considerably (30·6 to 38·4° C.).

(2) The skin temperature of the knee was also measured and was found to have a better correlation with the joint temperature; when the skin temperature was lowered to approximately 27° C. by body-cooling, the joint temperature fell to between 31 and 33·2° C., and when the skin temperature was raised to approximately 35° C. by body-warming, the joint temperature rose to between 37·0 and 38·4° C.

(3) The response of the joint temperature to the application of cold or heat to another part of the body depends apparently on the intensity, location, and duration of the temperature stimulus, since body-cooling and body-warming affect the temperature of a knee joint differently from the cold packs and hot packs applied to the contralateral knee by Horvath and Hollander (1949).

(4) Some speculations are made on the effect of body-cooling and body-warming upon blood flow to the joint and upon rheumatic disease.

REFERENCES

Abramson, D. I. (1944). "Vascular Responses in the Extremities of Man in Health and Disease", p. 98. University of Chicago Press.

Bard, P. (1941). *In* "Macleod's Physiology in Modern Medicine", ed. P. Bard, 9th ed., p. 862. Mosby, St. Louis.

Bazett, H. C. (1949). *In* "Physiology of Heat Regulation and the Science of Clothing", ed. L. H. Newburgh, pp. 163-168. Saunders, Philadelphia.

——, Love, L., Newton, M., Eisenberg, L., Day, R., and Forster, R., II (1948). *J. appl. Physiol.*, **1**, 3.

Bonney, G. L. W., Hughes, R. A., and Janus, O. (1952). *Clin. Sci.*, **11**, 167.

DuBois, E. F. (1948). "Fever and the Regulation of Body Temperature", p. 59. American Lecture Series, No. 13. Thomas, Springfield, Ill.

Fulton, J. F. (1949). "A Text-book of Physiology", 16th ed., p. 738. Saunders, Philadelphia.

Gibbon, J. H., Jr., and Landis, E. M. (1932). *J. clin. Invest.*, **11**, 1019.

Holbrook, W. P. (1953). *In* "Comroe's Arthritis", 5th ed., ed. J. L. Hollander, pp. 517-521. Lea and Febiger, Philadelphia.

Hollander, J. L., and Horvath, S. M. (1949). *Amer. J. med. Sci.*, **218**, 543.

——, Stoner, E. K., Brown, E. M., Jr., and DeMoor, P. (1951). *J. clin. Invest.*, **30**, 701.

Horvath, S. M., and Hollander, J. L. (1949). *Ibid.*, **28**, 469.

Landis, E. M., and Gibbon, J. H., Jr. (1933). *Arch. intern. Med.*, **52**, 785.

McKerslake, D. McK., and Cooper, K. E. (1954). *In* "Peripheral Circulation in Man", ed. G. E. W. Wolstenholme and J. S. Freeman, p. 115. Ciba Foundation Symposium. Churchill, London.

Montgomery, H., Naide, M., and Freeman, N. E. (1941). *Amer. Heart J.*, **21**, 780.

Pickering, G. W. (1932). *Heart*, **16**, 115.

Richards, R. L. (1946). "The Peripheral Circulation in Health and Disease", pp. 42-46. Livingstone, Edinburgh.

Selle, W. A. (1952). "Body Temperature. Its Changes with Environment, Disease, and Therapy", pp. 38-46. American Lecture Series, No. 147. Thomas, Springfield, Ill.

La température intra-articulaire du genou au cours de la vasoconstriction et vasodilatation cutanées des orteils chez des sujets normaux

RÉSUMÉ

(1) La température intra-articulaire du genou de sept sujets normaux fut mesurée pendant un état de vasoconstriction cutánée des orteils produit par refroidissement du corps, puis pendant un état de vasodilatation cutánée des orteils produit par réchauffement du corps. Avec la vasoconstriction cutanée par refroidissement du corps, la température intra-articulaire demeurait dans des limites étroites (31° à 33°2), mais avec la vasodilatation, la température articulaire variait considérablement (30°6 à 38°4).

(2) La température de la peau du genou fut aussi mesurée et révéla une meilleure corrélation avec la température articulaire; quand la température cutanée fut abaissée à environ 27° par refroidissement du corps, l'articulaire tomba entre 31° et 33°2, et quand la cutanée fut élevée à environ 35° par rechauffement du corps, l'articulaire s'éleva entre 37° et 38°4.

(3) La réponse de la température articulaire à l'application de froid ou de chaud à une autre région du corps depend apparemment de l'intensité, de la location et de la durée du stimulus calorique, puisque le refroidissement et le réchauffement du corps affectent

la température d'une articulation du genou d'une manière différente que l'application d'enveloppements froids ou chauds au genou contralatéral, procédé appliqué par Horvath et Hollander (1949).

(4) Quelques spéculations sont faites sur les effets du refroidissement et du réchauffement du corps sur l'irrigation sanguine du genou et sur la maladie rhumatismale.

La temperatura intra-articular de la rodilla en el curso de la vasoconstricción y vasodilatación cutáneas de los dedos del pie en sujetos sanos

SUMARIO

(1) Se midió en siete sujetos normales la temperatura intra-articular de la rodilla durante un estado de vasoconstricción cutánea de los dedos del pie producida al resfriar el cuerpo, y luego durante un estado de vasodilatación cutánea de los dedos del pie producida al calentar el cuerpo. Con la vasoconstricción cutánea por el resfriamiento del cuerpo, la temperatura intra-articular quedaba dentro de límites estrechos (31°a 33°2), pero con la vasodilatación ésta varíaba considerablemente (30°6 a 38°4).

(2) Se midío también la temperatura de la piel de la rodilla, revelando una mejor correlación con la temperatura articular; al bajar la temperatura cutànea a cerca de 27° por un resfriamiento del cuerpo, la de la articulación cayó entre 31° y 33°2 y al subirla a cerca de 35° por un calentamiento del cuerpo, la temperatura articular alcanzó 37° a 38°4.

(3) La respuesta de la temperatura articular a la aplicación del frío o del calor a otra parte del cuerpo depende aparentemente de la intensidad, del sitio y de la duración del estímulo calórico, ya que el resfriamiento y el calentamiento del cuerpo afectan la temperatura de una articulación de la rodilla de una manera diferente que la aplicación de envolturas frías o calientes a la rodilla contralateral, procedimiento empleado por Horvath y Hollander (1949).

(4) Se discuten algunas ideas acerca de los efectos del resfriamiento y del calentamiento del cuerpo sobre el riego sanguíneo de la rodilla y sobre la enfermedad reumática.

Ann. rheum. Dis. (1956), **15**, 246.

MODIFIED WAALER-ROSE REACTION EMPLOYING SENSITIZED HUMAN CELLS

BY

H. J. GIBSON AND N. R. LING

From the Bath Area Clinical Laboratories

(RECEIVED FOR PUBLICATION MAY 28, 1956)

The Waaler-Rose test (Waaler, 1940; Rose, Ragan, Pearce, and Lipman, 1948) has established itself as a laboratory procedure of limited value in the diagnosis of rheumatoid arthritis. With a few exceptions the workers who have used it find it to be positive in under 75 per cent. of cases of that disease. It is rarely positive in other conditions, except disseminated lupus erythematosus and hepatitis. Its importance appears to lie in the fact that it is independent of non-specific plasma protein changes which give the raised erythrocyte sedimentation rate, increased plasma viscosity, positive serum colloidal gold reaction, positive formol-gel test, and abnormal electrophoretic pattern not only in rheumatoid arthritis but in many other chronic diseases. The test has a relative specificity which leads to the hope that with a fuller understanding of its underlying principles a "break through" may be established in the problem of aetiology.

Many modifications have been introduced, but they have been mainly concerned with that part of the reaction represented by the patient's serum and the general conditions under which it reacts. An early refinement was the preliminary absorption of the serum by unsensitized sheep cells to remove natural anti-sheep haemolysin (Heller, Jacobson, and Kolodny, 1949). Attempts to isolate the active principle of the positive serum by fractionation have been numerous. Thus Svartz and Schlossmann (1953) claimed a high specificity for the cold-euglobulin fraction, and Robinson, Stulberg, and Kuyper (1954) and Ziff, Brown, Badin, and McEwen (1954), using the method of dialysis against solutions of low ionic strength, obtained the active principle in the euglobulin precipitate. Wager and Alameri (1953) also noted the low solubility of the factor. Hobson and Gorrill (1952) presented evidence that the agglutinating principle might be a thermostable complement fraction, and, by inference, suggested the ammonia-inactivable fourth component C 4. Heller, Jacobson, Kolodny, and Schuman (1952) and Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks (1955) found that various normal animal sera potentiated the reaction, and they devised a test using 5 per cent. (later 2 per cent.) sheep serum as diluent. Sheep serum was chosen as the most active of the animal species tested and not because the cells used were from that species. They made the important claim that under these conditions the strength of the reaction with normal sera was not dependent on the concentration of rabbit *v.* sheep amboceptor used to sensitize the cells as is the case with serum from rheumatoid cases. A four-fold or greater increase of titre in rheumatoid sera was noted with serum diluent as compared with saline diluent. Heller and others (1955) also employed Cohn's ethanol fractionation procedures in the analysis of the patient's serum effect and found that activity resided in Fraction III and probably in the beta-liproprotein part of that fraction. Heller, Jacobson, Kolodny, and Kammerer (1954) made a further advance in technique by adsorbing Fraction II (γ-globulin) from normal human serum on tanned sheep red cells and found that this could be substituted for the red cell-amboceptor system in a modified Rose test. An inhibitory factor in normal serum euglobulin absent from the serum of cases of rheumatoid arthritis, including those in which Waaler-Rose test is negative, has been demonstrated by Ziff and others (1954), who suggest that failure of the euglobulin to inhibit is a more sensitive indicator of the presence of agglutinating factor than the direct test. Heller and others (1954) also demonstrated an inhibitory effect following the addition of pooled Fraction II (γ-globulin) to positively reacting rheumatoid sera.

It has seemed to us that the test might be approached from the point of view of the "antigen". In its original form, the Rose test employed biological reagents from three species: sheep, rabbit,

and man. Rabbit and human sera may contain many reactive antigens and antibodies, and the serological system produced is thus of the utmost complexity.

The present work is concerned with the use of sensitized human red cells instead of the more usually employed sheep cells. In this way the species derivation of reagents could be cut down to two. It was felt that this simpler system would lend itself more readily to an analysis of the factors concerned. Hobson and Gorrill (1952) used sensitized guinea-pig and mouse cells in addition to those of sheep and obtained identical end-titres.

Winblad (1952) found that sensitized ox and horse cells gave a positive reaction, and Pike, Sulkin, and Coggeshall (1949) had employed ox and goat red cell systems successfully although human group-O red cells sensitized with homologous amboceptor were not agglutinated by one positive serum tested. Loghem-Langereis (1950, quoted by Jochem, Eyquem, and Jacqueline, 1955) was unsuccessful with a human red cell, rabbit anti-human system. Wager (1950), on the other hand, demonstrated that human Group-O cells could be substituted for sheep cells in the test and that the patient's own cells would also give the reaction. Dickgiesser and Harter (1953) reported that a potent anti-human red cell sensitizer could be prepared by immunizing rabbits with papain-treated human cells. Horse immune anti-human-red-cell serum has also been shown to be an effective sensitizer (Jochem and others, 1955). The general properties of the sensitized human red cell system in the Rose test have not hitherto been examined.

Materials and Methods

Patient's Serum.—All sera were stored at 4° C. and inactivated before use at 56° C. for 30 minutes. Storage over long periods was in the frozen state at −20°C. Controls were obtained from general medical and orthopaedic cases and from laboratory staff. Sera were tested by the original Rose technique in the routine clinical laboratory of the Royal National Hospital for Rheumatic Diseases employing sheep cells (Burroughs Wellcome) washed three times in normal saline and sensitized with one quarter of the minimal agglutinating dose (M.A.D.) of rabbit *v.* sheep serum (Difco).

Sensitized Human Red Cells.—A rabbit was immunized with Group-O Rh-negative cells from one of us (H.J.G.). The cells were collected in Alsever's solution and washed three times. The course consisted of seven intraperitoneal injections of 1 ml. and two intravenous injections of 5 ml. at two- or three-day intervals. When the titre was satisfactory (agglutination at 1 in 10,000) the animal was bled out by heart puncture under anaesthesia. 45 ml. of serum were obtained. This was stored, partly as a working solution in 50 per cent. glycerol at 4° C., and the remainder frozen at −20° C. For the test, human cells were washed and sensitized with one-quarter of the minimal agglutinating dose in a one per cent. red cell suspension. The original donor's cells were used except when the patient's cells were under test.

Haemagglutination Tests with Human Sera.—These were carried out exactly as in the original Rose test with doubling dilutions of the serum from 1 in 8 to 1 in 4,096 (final dilutions after adding red cell system). Tests were incubated for one hour at 37° C. and left overnight at 4° C. After a short period of incubation at 37° C. to exclude cold-agglutinins, tubes were shaken to read the end-point, which was shown by the presence of granules just visible to the naked eye. A check reading in doubtful cases can be usefully made after a further 15 minutes on the bench when normal sedimentation in negative tubes is commencing and a granular deposit in positive tubes is readily seen.

Fractionation of Human Sera.—The euglobulin method of Ziff (1954) was followed, except that no preliminary absorption was necessary. It was found that inactivation might be carried out before or after dialysis without difference to the result.

Results

When human red cells were sensitized with rabbit *v.* human amboceptor they could be used as a reagent in the Waaler-Rose test and appeared to give very similar results to those obtained with the sensitized sheep-cell reagent. Table I (overleaf) exemplifies the results. The end-titre obtained with human cells was usually very close to that of the classical Waaler-Rose reaction. In the example chosen in Table I, the serum was a strong reactor with a D.A.T. of 256. The end-titre with human cells proved to be exactly the same as that with sensitized sheep cells. In some tests human cells gave a higher result, in others lower, but the difference was rarely more than two tubes.

The patient's own cells were an equally efficient reagent, and in such a reaction all question of natural, or iso-antibodies could be excluded. It is of interest that the sensitized cells of the patient were fully agglutinable after washing, because in this reaction the only antigenically foreign material is the adsorbed haemagglutinating antibody. The patient's serum has been tested against his own sensitized cells in ten cases.

Comparison of Sheep and Human Sensitized Red Cells as Reagents

(1) *Correlation with Results of Sensitized Sheep Cell Reactions.* At this stage it has not been possible to undertake a large-scale correlation between the clinical condition and the human red cell reaction.

TABLE I

COMPARISON OF AGGLUTINATION TESTS WITH SHEEP, HUMAN, AND PATIENT'S OWN RED CELLS, AND EFFECT OF WASHING

Cells		Dilution of Patient's Serum (Case of Active Rheumatoid Arthritis)									
		1:8	16	32	64	128	256	512	1,024	2.048	4,096
Sheep	Sensitized ..	+++	+++	+++	+++	+++	+++	+++	+++	+	–
	Unsensitized	+	–	–	–	–	–	–	–	–	–
Human (H.J.G.: O Rh Negative)	Sensitized ..	+++	+++	+++	+++	+++	+++	+++	+++	+	–
	Unsensitized	–	–	–	–	–	–	–	–	–	–
Human (Patient)	Sensitized ..	+++	+++	+++	+++	+++	+++	+++	+++	+	–
	Unsensitized	–	–	–	–	–	–	–	–	–	–
Human (Patient)	Sensitized and Washed	+++	+++	+++	+++	+++	+++	+++	+++	+	–

It was thought more informative to correlate the sheep-cell with human-cell results, because there is already an extensive literature, reviewed by Bunim, Sokoloff, Williams, and Black (1954), relating the former to rheumatoid arthritis, lupus erythematosus, hepatitis, and other diseases. In all, one hundred specimens have been tested in parallel by the two methods. The results (Table II) show a high degree of correlation. Where disagreement is present the figures show a slightly higher sensitivity in the human cell test. In the original Rose test a differential titre of 16 occupies a zone between positive and negative and it is of interest that the human cell test gives both positive and negative results at this titre.

TABLE II

CORRELATION BETWEEN HUMAN AND SHEEP CELL TESTS ON 100 PATIENTS' SERA ALL CLINICAL GROUPS

Sensitized Sheep Cells D.A.T.	Sensitized Human Cells		
	Positive 1 in 8	Negative	Total
Negative (<1:8) ..	2	46	48
Borderline (16) ..	7	6	13
Positive (>1:16) ..	39	0	39
Total Sera ..	48	52	100

(2) *Distribution in Serum Fractions.*—Further evidence that the tests are basically the same is given in Table III, in which positively reacting and normal sera were compared before and after fractionation. The two human-cell systems gave the same results throughout, the euglobulin fraction being as powerful as the whole serum. The fall in titre for sheep cells is not significant, other experiments frequently showing an equal titre.

TABLE III

AGGLUTINATION REACTIONS USING EUGLOBULIN FRACTIONS OF RHEUMATOID AND NORMAL SERA WITH HUMAN AND PATIENT'S CELLS

Sensitized Cells (¼ M.A.D.)	Serum of Patient E		Normal Serum	
	Reciprocal Titre of Whole Serum	Reciprocal Titre of Euglobulin	Reciprocal Titre of Whole Serum	Reciprocal Titre of Euglobulin
Human (H.J.G.)	2,048	2,048	0	0
Patient E ..	2,048	2,048	0	0
Sheep*	2,048	1,024	8	8

* In tests using sheep cells, sera were absorbed by unsensitized sheep cells before testing.

(3) *Absorption of the Serum Principle reacting with Sensitized Human Cells.*—Absorption by unsensitized human cells did not influence the patient's serum titre. Sensitized cells gave some evidence of an absorption effect, but it was achieved only with difficulty. Multiple serial absorptions of the same sample of human positive serum were tried, 2 ml. of packed sensitized human cells were added to 4 ml. of positive serum and were allowed to interact at 37° C. for one hour and left overnight at 4° C. The serum was separated and an aliquot tested for agglutinating activity. The remainder was reabsorbed in the same way and again tested. Table IV (opposite) shows the results of an experiment in which three absorptions were carried out. The titre fell from 256 to 64. Some of this fall may have been due to dilution in the absorbing process.

The effect of varying the sensitizing dose was then tested. Human cells were used, unsensitized, and sensitized by one-tenth, one-quarter, and one minimum agglutinating dose of the homologous antiserum. Absorption of a known positive serum

TABLE IV

MULTIPLE SERIAL ABSORPTIONS OF SAME SAMPLE OF ROSE POSITIVE SERUM BY SENSITIZED HUMAN RED CELLS

(Red cells sensitized by ¼ M.A.D. ambocepter)

Treatment of Patient's Serum	End Titre
Untreated	256
After First Absorption	128
After Second Absorption	128
After Third Absorption	64

was carried out overnight at 4° C. with an equal volume of packed sensitized human cells. The results are shown in Table V.

TABLE V

EFFECT OF ABSORPTION OF RHEUMATOID SERUM WITH SENSITIZED HUMAN CELLS ON WAALER-ROSE TITRE

Sensitizing Dose (× M.A.D.) on Cells used for Absorption*	Titre of Rheumatoid Serum
Nil	128
0·1	64
0·25	32
1·0	16

* Absorption was performed overnight at 4° C. with an equal volume of packed human cells sensitized with the stated fraction of the minimum agglutinating dose (M.A.D.).

Absorption in all cases was incomplete, but the reduction in serum titre ran parallel with the sensitizing dose of amboceptor. This finding recalls the conclusion of Heller and others (1954) that the sensitizing substance acts in the context of these procedures as antigen and the agglutinating factor in a rheumatoid sera as antibody. The point is one of cardinal importance in the understanding of the mechanism of the test and further work is required. The difficulty of effecting absorption of the reactive principle has been previously noted in tests with sheep cells by Waaler (1940), Winblad (1952), Pike and others (1949), and Tawil and Abd el Wahab (1955). Heller and others (1954) were able to absorb "agglutinins" for cells sensitized by both amboceptor and Fraction II by treating the serum with Fraction II-sensitized cells. The effect on the efficiency of absorption of increasing the sensitizing dose was noted by Wager (1950) and Pike and others (1949) in the case of the sheep-cell reaction.

Discussion

Sensitized human cells form a suitable reagent for the Waaler-Rose test, and the patient's own cells may be used. By this means the system is simpler from a serological point of view, as an antigenically foreign biological reagent has been eliminated. From a number of tests carried out, the human-cell system appears to give very similar results to those obtained with sheep cells. We find no evidence that any spectacular increase in the incidence of positive reactions in rheumatoid arthritis will be found with human cells.

The use of patient's cells for a modified Waaler-Rose test has certain advantages. It requires only preserved anti-human haemagglutinating serum and patient's clotted blood. The red cells, the most labile of the reagents used in the test, can be of known freshness, and preliminary absorption of patient's serum is unnecessary. At present, however, the modification is not put forward as a routine procedure to replace the standard test, but rather as a research tool for the investigation of the principles underlying it.

Our results strongly suggest that the serum factor reacting with sensitized human Group-O or with the patient's own cells is the same as that which reacts with sensitized sheep cells in the classical Waaler-Rose test. From a consideration of the literature of this test, the fundamental question is whether the agglutinin-activating factor is a true serological reagent of antibody type or a substance with biochemical activity resembling an enzyme. It is towards the solution of this problem that the human red cell system is proposed. When the patient's own washed sensitized cells react with his own serum, the serological system is a relatively simple one. The only foreign protein is the adsorbed antibody globulin which could act as "antigen" in the test. It has, however, been shown by others that amboceptors derived from guinea-pig and horse are equally effective in sensitizing sheep cells for the test, and it may be presumed that these animal species could also provide specific anti-human red-cell sensitizers with the same effects. We are, therefore, faced with the necessity of postulating an "antibody" in rheumatoid arthritis capable of reacting with the adsorbed antibody globulin of a variety of animal species. If such a remarkable polyvalency is to be proved, or if, alternatively, a common antigen is to be demonstrated in antibody globulins of a variety of unrelated animal species, the simplest possible reacting system is desirable. We wish to emphasize the value of a human Group-O sensitized cell reagent, and especially of one using the patient's own red cells in clarifying the problems which arise as to the mechanism of the test.

Any hypothesis put forward to explain the mechanism of the Waaler-Rose test must take into account the fact that the patient's own red cells can replace those of sheep.

Summary and Conclusions

(1) The observation has been confirmed that the Waaler-Rose test may be carried out with human red cells sensitized by a rabbit *v.* human amboceptor in the same dosage (¼ M.A.D.) as is used in the original test.

(2) The patient's own red cells sensitized and washed are agglutinated in the same way as sensitized cells from any group-O Rh negative human, indicating that iso-antibodies have no part in the reaction.

(3) As with the sheep cell system, the patient's serum activity resides in the euglobulin fraction.

(4) Absorption of the serum effect by the use of sensitized cells is difficult to achieve. In the present work the authors were partially successful when multiple serial absorptions were carried out on the same serum sample, or when the dose of sensitizer was increased above that used in the test. The absorption effects were unlike those associated with simple antigen-antibody reactions.

We are indebted to Miss P. P. Walpole for her valuable technical assistance in all stages of this work.

REFERENCES

Bunim, J. J., Sokoloff, L., Williams, R. R., and Black, R. L. (1955). *J. chron. Dis.*, **1**, 168.

Dickgiesser, F., and Harter, F. (1953). *Z. ges. exp. Med.*, **122**, 221.

Heller, G., Jacobson, A. S., and Kolodny, M. H. (1949). *Proc. Soc. exp. Biol.*, **72**, 316.

——, ——, ——, and Kammerer, W. H. (1954). *J. Immunol.*, **72**, 66.

——, ——, ——, and Schuman, R. L. (1952). *Ibid.*, **69**, 27.

——, Kolodny, M. H., Lepow, I. H., Jacobson, A. S., Rivera, M. E., and Marks, G. H. (1955). *Ibid.*, **74**, 340.

Hobson, D., and Gorrill, R. H. (1952). *Lancet*, **1**, 389.

Jochem, E., Eyquem, A., and Jacqueline, F. (1955). *Ann. Inst. Pasteur*, **88**, 625.

Loghem-Langereis, P. E. van (1950). "Serological Reactions in Rheumatic Disease". Thesis, Amsterdam.

Pike, R. M., Sulkin, S. E., and Coggeshall, H. C. (1949). *J. Immunol.*, **63**, 441, 447.

Robinson, A. R., Stulberg, C. S., and Kuyper, A. C. (1954). *Proc. Soc. exp. Biol.*, **85**, 4.

Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Ibid.*, **68**, 1.

Svartz, N., and Schlossmann, K. (1953). *Acta med. scand.*, **146**, 313.

Tawil, G. S., and Abd el Wahab, E. M. (1955). *Amer. J. clin. Path.*, **25**, 166.

Waaler, E. (1940). *Acta path. microbiol., scand.*, **17**, 172.

Wager, O. (1950). *Ann. Med. exp. Biol. Fenn.*, **28**, Suppl. 8.

——, and Alameri, E. (1953). *Ibid.*, **31**, 361.

Winblad, S. (1952). *Acta med. scand.*, **142**, 458.

Ziff, M., Brown, P., Badin, J., and McEwen, C. (1954). *Bull. rheum. Dis.*, **5**, 75.

La réaction de Waaler-Rose modifiée, employant des globules humains sensibilisés

RÉSUMÉ

(1) On confirme l'observation que la réaction de Waaler-Rose peut être exécutée avec des globules rouges humains sensibilisés par un ambocepteur lapin antihumain avec la même dose (un quart de la dose minime agglutinante) qu'on utilise dans la réaction originale.

(2) Les propres globules rouges du malade, sensibilisés et lavés, sont agglutinés de la même manière que les globules sensibilisés de n'importe quel groupe humain O, Rh-négatif, ce qui indique que les anticorps homologues ne participent pas à la réaction.

(3) Comme dans la méthode utilisant les globules de mouton, l'activité du sérum du malade réside dans la fraction d'euglobuline.

(4) L'absorption de l'effet du sérum par l'emploi de globules sensibilisés est difficile. Dans ce travail particulier les auteurs eurent des succès partiels en exécutant des absorptions multiples en série sur le même prélèvement, ou bien en excédant la dose habituelle du sensibilisateur. Les effets de l'absorption ne ressemblaient pas à ceux associés à de simples réactions entre l'antigène et l'anticorps.

La reacción de Waaler-Rose modificada, empleando globulos humanos sensibilizados

SUMARIO

(1) Se confirma la observación que la reacción de Waaler-Rose puede ejecutarse con glóbulos rojos humanos sensibilizados por un amboceptor de conejo antihumano con la misma dosis (un cuarto de la dosis mínima aglutinante) que se suele emplear en la reacción original.

(2) Los propios glóbulos rojos del enfermo, sensibilizados y lavados, se aglutinan de la misma manera que los glóbulos de cualquier grupo humano O, Rh negativo, lo que indica que los iso-anticuerpos no participan en la reacción.

(3) Como en el sistema de glóbulos de oveja, la actividad del suero del enfermo mora en la fracción de euglobina.

(4) La absorción del efecto sérico por el empleo de glóbulos sensibilizados se alcanza con dificuldad. En este trabajo los autores tuvieron éxito parcial, ejecutando absorciones multiples seriales sobre el mismo especimen sérico o excediendo la dosis habitual del sensibilizador. Los efectos de la absorción no se parecían a los asociados a simples reacciones entre el antígeno y el anticuerpo.

Ann. rheum. Dis. (1956), **15**, 251.

CHLOROQUINE AND RHEUMATOID ARTHRITIS
A SHORT-TERM CONTROLLED TRIAL

BY

A. FREEDMAN
Hackney Hospital, London

(RECEIVED FOR PUBLICATION JUNE 20, 1956)

When Page (1951) reported that mepacrine produced improvement in lupus erythematosus, he stated that, in one of his patients, a rheumatoid type of arthritis which had been present for 2 years improved together with the skin lesions. Following this report, I began an investigation of the treatment of rheumatoid arthritis with mepacrine (Freedman and Bach, 1952). Early results were promising, but a controlled trial was not possible because the drug almost invariably discoloured the skin. A pilot investigation with other antimalarials suggested that Proguanil was of doubtful value, but that chloroquine seemed to give benefit with absence of toxic reactions*. The controlled trial with chloroquine was begun in April, 1953.

Procedure

Patients.—In order to obtain a sufficient number of patients for the investigation from one rheumatism centre it was unfortunately necessary to include cases which varied considerably as regards duration of disease and extent and severity of joint involvement. A total of 69 patients who showed acute manifestations of the disease which included active inflammation of at least four joints were taken into the trial, and randomly distributed into two groups. One group received chloroquine and the other dummy tablets. These cases were admitted to the trial over a period of 2 years, and the following observations refer to the first 16 weeks of treatment, after which nearly all patients received chloroquine as their standard treatment.

Treatment.—During the trial period all patients received eight 5-gr. tablets of enteric-coated aspirin and 200 mg. of ascorbic acid daily. If they were anaemic, oral iron was also prescribed. With regard to the chloroquine or control tablets, the physician did not know which type of treatment each patient was to receive but merely numbered each case in order of the first attendance. The dispenser followed a random list and dispensed either Q or R tablets according to the case number, not knowing which was the active preparation. The first forty patients took one tablet daily, either chloroquine sulphate, 200 mg., or the control tablet of similar appearance. Because experience with chloroquine outside the trial suggested that a dose of 300 mg. daily was more effective, the remaining patients were given 1½ tablets daily.

Assessment.—The patients were examined at a special clinic held on a separate afternoon for this purpose. At each visit they were weighed and blood was taken for haemoglobin, erythrocyte sedimentation rate, and liver function tests. They were asked specific questions concerning their mood, appetite, sleep, and strength, their pain and stiffness, and their need for analgesics other than the tablets routinely prescribed. They were asked about any change in their ability to dress and wash, to work, or to carry out household chores and handicrafts. Special note was made of their facies and colour, the presence or absence of oedema of the legs, palmar erythema, Raynaud's phenomenon, nodules, lymph glands, and rashes.

Temporo-mandibular, clavicular, and manubrial joints, and the spine, as well as all the limb joints, were separately examined.

Swelling was assessed arbitrarily in three grades.

Joint tenderness was graded 1, 2, or 3: 1 representing tenderness, 2 wincing, and 3 withdrawal of the affected part. The sum of these tenderness figures was then recorded as total tenderness.

Power of grip was measured on a mercury sphygmomanometer by the patient exerting as much pressure as he could on the folded cuff distended to a pressure of 30 mm. Hg.

The time taken to walk twice the length of a corridor (40 yds) was recorded.

The dexterity of the hands was measured by recording the time taken to insert a lace in and out of the holes on one side of a boot.

The patients were assessed every 2 or 3 weeks. At the end of the trial these records provided figures expressing joint inflammation and joint function, and data from which subjective and objective clinical assessments could be made.

* This was reported to the Heberden Society on December 5, 1953 (*Annals of the Rheumatic Diseases* (1954), **13**, 74).

Material

There were 35 patients in the control group and 34 in the chloroquine group. In the control group, seven patients defaulted (two at 2 weeks, one at 4 weeks, one at 6 weeks, two at 8 weeks and one at 13 weeks). In the chloroquine group there were no defaulters during the period of the trial. One patient had treatment discontinued at 6 weeks because she developed a psychosis. The omission of all defaulters from the final analysis was thought inadvisable because they were all in the control group and their default might have been due to lack of progress. Therefore, patients who had treatment for 6 weeks or longer—by which time some response would have been apparent—were retained in the groups for analysis.

The final numbers of cases were 32 in the control group and 34 in the chloroquine group, and the age and sex distributions were similar (Table I).

TABLE I

AGE AND SEX DISTRIBUTION

Therapy		Control		Chloroquine	
Sex		Male	Female	Male	Female
Age Group (yrs)	–39	2	6	0	5
	40–49	1	3	4	2
	50–59	3	9	3	8
	60–	3	5	3	9
	All Ages	9	23	10	24

Table II gives the distribution of patients according to the duration of the disease when treatment was begun. The chloroquine group contained slightly more patients with recent disease. There were eleven patients in the chloroquine group and seven in the control group with disease of less than one year's duration.

TABLE II

DURATION OF DISEASE WHEN TREATMENT WAS BEGUN

Therapy		Control		Chloroquine	
Sex		Male	Female	Male	Female
Duration of Disease (yrs)	Less than 1	4	3	7	4
	1–4	5	7	2	9
	5–9	1	3	1	6
	10–	0	9	0	5

For various reasons (holidays, non-attendance, late default, etc.), the duration of the trial period of treatment was not always the 16 weeks originally planned. Table III gives the distribution of the duration of treatment in the two groups. The chloroquine group, on the average, received longer treatment than the control group, the mean being 16 weeks for the former and 14·9 weeks for the latter.

TABLE III

DURATION OF TREATMENT

Therapy		Control	Chloroquine
Duration of Treatment (wks)	6– 7	1	1
	8–11	4	1
	12–15	7	7
	16–	20	25
	Total	32	34
	Average	14·9	16

Results

(*a*) *Joint Tenderness.*—Table IV (opposite) records the ranges of joint tenderness at the beginning and end of the treatment. The tenderness declined in both groups but more so in the chloroquine group. Thus, of the seven control patients with total tenderness of less than 10, only one had lost all tenderness at the end of the trial, whereas of the four patients with this initial tenderness who received chloroquine, two patients lost all tenderness by the end of the trial. It will also be observed that there were four control patients and nine chloroquine patients with initial tenderness of 30 or more, but at the end of the trial there were five control patients and only one chloroquine patient with this degree of tenderness. The overall averages for joint tenderness at the beginning were 19·0 in the control group and 23·5 in the chloroquine group, falling to 16·2 and 10·1 respectively by the end of the treatment. The mean improvement in the chloroquine group was statistically significant ($t=6·65$; $P<0·001$).

(*b*) *Strength of Grip.*—The mean strength for the 32 controls at the start of treatment was 134·1, rising to 139·9 mm. Hg at the end of the trial. The figures for the chloroquine-treated group were 129·8, rising to 155·3 mm. Hg. The amount of improvement in those receiving chloroquine was statistically significant ($t=5·90$, $P<·001$).

TABLE IV
NUMBER OF PATIENTS WITH GIVEN DEGREE OF TENDERNESS AT END OF COURSE OF TREATMENT RELATED TO INITIAL RANGE OF TENDERNESS

Range of Initial Tenderness	Therapy	No. of Patients	Range of Joint Tenderness at End of Course				
			0	1–9	10–19	20–29	30–
Less than 10	Control	7	1	6			
	Chloroquine	4	2	2			
10–19	Control	11	0	6	2	3	
	Chloroquine	10	1	6	2	1	
20–29	Control	10	0	2	4	2	2
	Chloroquine	11	0	5	4	2	0
30–	Control	4	0	0	0	1	3
	Chloroquine	9	1	1	4	2	1
Total	Control	32	1	14	6	6	5
	Chloroquine	34	4	14	10	5	1

TABLE V
NUMBER OF PATIENTS SHOWING GIVEN CHANGE IN STRENGTH OF GRIP (mm./Hg) FROM BEGINNING TO END OF TREATMENT

Therapy	No. of Patients	Improved		No change (+ or − 10 mm./Hg)	Deteriorated	
		by 50 mm./Hg or more	by 10–50 mm./Hg		by 10–50 mm./Hg	by 50 mm./Hg or more
Control	32	5	10	9	3	5
Chloroquine	34	4	19	8	3	0

Table V places the patients according to the degree of improvement or deterioration in strength of grip and illustrates the difference between the two groups.

(*c*) *Function Tests.*—Table VI gives the times taken in the lacing and walking tests in the two groups. Only the lacing time of the chloroquine-treated group shows significant improvement, (average improvement 7·0, $t=4·79$; $P<0·001$). The average walking times for the two groups were not significantly shortened.

TABLE VI
AVERAGE TIME TAKEN TO LACE ONE SIDE OF A BOOT AND TO WALK 40 YARDS

Ability Measured	Therapy	Number of Patients	Average Time (sec.)	
			Start	End
(*a*) Lacing*	Control ..	29	39·0	36·4
	Chloroquine ..	30	39·5	32·5†
(*b*) Walking	Control‡ ..	31	41·8	38·4
	Chloroquine ..	34	44·9	41·3

* Not all the patients were so tested.
† Improvement statistically significant.
‡ Excluding one patient who could barely walk the requisite distance.

(*d*) *The Score.*—A tenderness and function score was obtained by awarding 50 if there was no tenderness (*i.e.* $\frac{100-0}{2}$), 25 if the grip was 200 mm. Hg or more (*i.e.* $\frac{200}{8}$), and 25 if the walking time was 20 sec. (*i.e.* $\frac{70-20}{2}$), making a total of 100, or less if there was tenderness, weakness of grip, or slowness in walking. For example, if a patient had a total tenderness of 24, a grip of 160 mm. Hg, and a walking time of 40 sec., he was awarded $\frac{100-24}{2}+\frac{160}{8}+\frac{70-40}{2}$, *i.e.* a score of 73.

Table VII (overleaf) gives the number of patients at different levels at the beginning and end of treatment. Although the chloroquine group started at a rather lower mean level, they finished at a higher mean level than the control group. The mean change for the control group was only +2·4, while for the chloroquine group there was an improvement of +11·6, which is statistically significant ($t=7·02$; $P<·001$).

TABLE VII

(*a*) NUMBER OF PATIENTS AT DIFFERENT LEVELS OF SCORE AT THE START AND END OF TREATMENT

(*b*) MEAN SCORE AT START AND END OF TREATMENT

Therapy		Control		Chloroquine	
No. of Patients		At Start	At End	At Start	At End
(*a*) Range of Score:	– 59	5	5	11	3
	60– 79	17	11	15	13
	80–100	10	16	8	18
		32	32	34	34
(*b*) Mean of Score		73·0	75·4	67·6	79·2*

* Statistically significant.

(*e*) *Haemoglobin Levels and Blood Sedimentation Rate.*—Table VIII gives the average figures at the beginning and end of treatment. Changes were slight and there were no appreciable differences between the two groups.

TABLE VIII

HAEMOGLOBIN AND ERYTHROCYTE SEDIMENTATION RATE

Characteristic	Therapy	Number of Patients	Average Measurement	
			Start of Treatment	End of Treatment
Hb (per cent.)	Control ..	32	78·3	79·7
	Chloroquine ..	34	77·8	79·2
E.S.R. (mm./hr Wintrobe)	Control ..	32	36·4	34·3
	Chloroquine ..	34	40·1	36·5

(*f*) *Clinical Assessment.*—Owing to the short period of the trial it was not possible to employ the criteria of the American Rheumatic Association (Steinbrocker, Traeger, and Batterman, 1949) to express the degree of improvement achieved.

The recorded clinical data made it possible to judge the progress of each patient for the period of the trial, and also to give an assessment of the patient's own view of his improvement or deterioration. These objective and subjective impressions are given in Table IX. They show close agreement and indicate a clear advantage to the patients receiving chloroquine. Definite deterioration occurred in five of the control group and in none of the chloroquine group.

(*g*) *Toxic Effects.*—One patient receiving chloroquine developed delusions and euphoria after 6 weeks. When the tablets were discontinued the symptoms still persisted; she was an elderly woman and it would seem very unlikely that the chloroquine was responsible.

Eighteen of the control subjects gained weight during the trial period, and twelve lost weight. In the chloroquine-treated group, nine patients gained weight and twenty patients lost weight.

There was thus a mean rise of 1·2 lb. in the control group and a mean fall of 1·6 lb. in the chloroquine group. Loss of weight is a feature of activity of rheumatoid arthritis, and these figures indicate that the weight was lost while patients were improving on chloroquine, and suggest that the drug was responsible.

In the chloroquine-treated group two patients had a recurrence of eczema that they had had before, one patient had a transient rash on his hands, one had eczema on one leg, and one had some irritation of his hands.

In the control group one patient complained of pruritus, one had a recurrence of eczema, and a third had transient irritating papules on the forearms. In all cases the rash was slight and localized and was not sufficiently troublesome to stop the treatment.

Discussion

Trial.—Previous experience having suggested that improvement began before the 6th week of treat-

TABLE IX

SUBJECTIVE AND OBJECTIVE IMPRESSIONS OF RESPONSE TO TREATMENT

Impression	Therapy	Number of Patients	Grades of Response to Treatment*							
			+IV	+III	+II	+I	in statu quo	−I	−II	−III
Subjective	Control ..	32	1	6	5	8	3	4	3	2
	Chloroquine ..	34	2	11	13	2	3	3	0	0
Objective	Control ..	32	1	7	4	4	4	7	3	2
	Chloroquine ..	34	2	6	14	8	2	2	0	0

* +IV = full restoration of function without symptoms.
+III = greatly improved.
+II = moderately improved.
+I = slightly improved.
−I = slightly worse.
−II = moderately worse.
−III = much worse.

ment, 16 weeks was chosen as the trial period for each patient in the hope that clear-cut improvement would take place in that time. Numerical assessment of joint tenderness and of the tests of function, together with subjective and objective clinical assessments, provided the measure of progress. Analysis of the figures for joint tenderness, grip, and lacing time shows that the chloroquine group improved significantly whereas in the control group improvement was slight and not significant. The two groups were not perfectly matched, for it so happened that the chloroquine group contained rather more patients with disease of recent onset, with slightly more active disease (as judged by erythrocyte sedimentation rate, extent of tenderness, and function tests), and a slightly longer period of treatment. These differences taken separately were not significant, but it might be held that taken together they would permit the chloroquine-treated group to make greater progress than the control group within the period of the trial. However, assessment according to the duration of the disease shows that in the control group only patients with disease of less than 6 months duration improved almost as much as the chloroquine-treated patients. Comparison of patients with identical periods of treatment shows a similar difference between response to chloroquine and the control tablets as that seen in the two groups as a whole.

The lack of change in haemoglobin and E.S.R. is attributed to the short period of the trial course of treatment.

Long-Term Therapy.—It must be stressed that the improvement shown in the chloroquine-treated group was only moderate, having taken place gradually during the 16 weeks' period of the trial.

Of the 54 patients who remain under observation, 50* received chloroquine after the trial. Of these 43 have become really well; that is, they have no stiffness, and any pain that occurs can reasonably be attributed to use of joints affected by secondary degenerative changes. They have no evidence of joint inflammation, but may have a raised erythrocyte sedimentation rate. They have little or no need for analgesics. Three patients have slight joint inflammation, three were taken off chloroquine fairly early because of lack of adequate response, and one still has active disease despite chloroquine.

* After the trial period of treatment six further patients defaulted:
three were not receiving chloroquine,
one was on Butazolidin, having gone directly on to this drug after the control tablets;
one was on chloroquine, having improved;
one after a year on chloroquine when he was quite well.
Two other patients died:
one was the patient with a psychosis, already mentioned;
the other, after a course of control tablets, was given chloroquine but defaulted after 5 weeks, and 6 months later died of nephritis.

Observations of these patients and of others treated outside the trial suggests that 200 mg. daily might not be enough to control joint inflammation in all cases. An increase in the dose to 300 mg., and rarely to 400 mg. daily, may be necessary. Cessation of therapy may lead to a relapse within a few months. This seems more likely to occur if the disease is of long standing. Where the arthritis has been present for a few months only, and erythrocyte sedimentation rate has fallen to normal, relapse has not so far occurred.

Toxic Effects.—Nausea and vomiting and difficulty in visual accommodation have been described as toxic reactions to chloroquine. Though not observed during the trial they were present in some patients during subsequent treatment with chloroquine; in a few it was necessary to reduce the dosage, but treatment with chloroquine was not stopped on this account. Nor was treatment stopped where there was a decline in body weight or in the few patients who had pruritus or a mild limited dermatitis. This minor incidence of side-effects with chloroquine is in sharp contrast to my experience with mepacrine, where rashes were frequent and severe.

Deaths due to aplastic anaemia have occurred in patients given mepacrine for lupus erythematosus (Sawicky, Kanof, Silverberg, Braitman, and Kalish, 1952; Paton, Riddell, and Strong, 1955). I have knowledge of one patient with rheumatoid arthritis who died of aplastic anaemia after mepacrine treatment, and I had two arthritics who have fortunately recovered. It would seem that patients with arthritis or lupus erythematosus are more susceptible to the development of this dreaded toxic effect than are healthy individuals receiving mepacrine as a prophylactic against malaria. Chloroquine is now preferred in the treatment of lupus erythematosus (Goldman, Cole, and Preston, 1953; Stoughton, 1955).

Rationale.—Haydu (1949) believes that the tissue requirements of adenosine triphosphate (ATP) are increased in rheumatoid arthritis. He believes that chloroquine gives benefit because it inhibits the ATP-ase activity (Haydu, 1954).

My own interest in anti-malarials was due to the tentative notion that they might act as chemotherapeutic agents against a hypothetical organism primarily responsible for the disease—a hypothesis which has yet to be made untenable. I do not know that Hench has shifted away from the statement that he made nearly 20 years ago: "As a practising clinician I have committed myself, with reservations, to the microbic theory" (Hench, 1938).

Kuzell, Gardner, Fairley, and Tripi (1952) screened a large number of antibiotics and chemotherapeutic agents to determine their value in an experimental arthritis in rats produced by a pleuronomonia-like organism. Mepacrine did not help, but gold, aureomycin, and Pentaquine were beneficial.

Brennecke, Alving, Arnold, Bergenstal, and De Wind (1951) studied Primaquine and three related 8-amino quinolines in the treatment of rheumatoid arthritis and thought that they had anti-rheumatic activity. However, toxic effects were common and they suggested further exploration of this group of compounds. Mepacrine and chloroquine are 4-amino quinoline compounds which in general are less toxic than the 8-amino quinolines.

Summary

66 patients suffering from active rheumatoid arthritis were allocated at random in almost equal numbers to treatment for 16 weeks with either chloroquine or a similar dummy tablet. Although the two groups were not perfectly matched, there was no significant difference between them in respect of duration or severity of disease. The physician himself was unaware of the type of treatment that each patient was receiving. All the patients were also given 40 gr. aspirin daily and appropriate physiotherapy. During the early part of the trial 200 mg. chloroquine sulphate was given daily, but later the dose was increased to 300 mg. A numerical basis for subjective and objective clinical assessment was devised, and this showed that the control group improved only slightly whereas the group treated with chloroquine made a significant though not substantial improvement. No change was observed in haemoglobin and erythrocyte sedimentation rate, and this was attributed to the shortness of the trial period.

The progress of the patients subsequently treated with chloroquine, fifty in all, was satisfactory. Only one had no clear response, despite long-continued treatment, and three others were taken off the drug early because of lack of adequate response. No toxic effect of any significance was noted in patients treated with 300 mg. chloroquine sulphate daily for 2 years.

The trial, though not giving conclusive proof of the long-term value of chloroquine in rheumatoid arthritis, does give sufficient data to warrant a larger investigation.

I wish to thank Dr. Francis Bach, Consultant Rheumatologist to Hackney Hospital, for his interest and for permission to treat his patients.

I am greatly indebted to Dr. J. T. Boyd of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, for his help in planning the investigation and for analysing the results.

I must also thank Sister Joan Hornsby for her diligence in the management of the special clinic.

Messrs. May and Baker, Ltd., kindly provided the special tablets of chloroquine sulphate (Nivaquine) and the control tablets.

REFERENCES

Brennecke, F. E., Alving, A. S., Arnold, J., Bergenstal, D. M., and De Wind, L. T. (1951). *J. Lab. clin. Med.*, **38**, 795.
Freedman, A., and Bach, F. (1952). *Lancet*, **2**, 321.
Goldman, L., Cole, D. P., and Preston, R. H. (1953). *J. Amer. med. Ass.*, **152**, 1428.
Haydu, G. G. (1949). *Amer. J. occup. Ther.*, **3**, 177.
—— (1953). *Amer. J. med. Sci.*, **225**, 71.
—— (1954). *Rheumatism*, **10**, 32.
Hench, P. S. (1938). *In* "A Survey of Chronic Rheumatic Diseases," ed. R. G. Gordon and others, p. 35. Oxford University Press.
Kuzell, W. C., Gardner, G. M., Fairley, D. M., and Tripi, H. B. (1952). "Rheumatic Diseases": based on "Proc. VII Int. Congr. Rheum. Dis.", p. 409. Saunders, Philadelphia.
Page, F. (1951). *Lancet*, **2**, 755.
Paton, M. D., Riddell, M. J., and Strong, J. A. (1955). *Lancet*, **1**, 281.
Sawicky, H. H., Kanof, N. B., Silverberg, M. G., Braitman, M., and Kalish, B. (1952). *J. invest. Derm.*, **19**, 397.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.
Stoughton, R. B. (1955). *Illinois med. J.*, **107**, 299.

La chloroquine et l'arthrite rhumatismale

RÉSUMÉ

Soixante-six malades, souffrant d'arthrite rhumatismale évolutive, furent désignés au hasard, en nombres presque égaux, pour être traités durant seize semaines, soit à la chloroquine, soit avec des comprimés similaires factices. Bien que les deux groupes ne fussent pas parfaitement assortis, il n'y avait pas de différence significative entre eux en ce qui concerne la durée ou la sévérité de la maladie. Le médecin lui-même était dans l'ignorance du type de traitement que chaque malade recevait. Tous les malades reçurent aussi 2,6 grammes d'aspirine quotidiennement ainsi que la physiothérapie adéquate. Durant la première partie de l'essai, 200 mg. de sulphate de chloroquine furent administrés quotidiennement, mais ensuite la dose fut augmentée jusqu'à 300 mg. Une base numérique élaborée pour une évaluation clinique subjective et objective, permit de constater que le groupe-témoin ne faisait que des progrès légers alors que le groupe traité à la chloroquine faisait des progrès significatifs, bien que non substantiels. Aucun changement ne fut constaté dans le vitesse de sédimentation érythrocytaire et le taux d'hémoglobine, et ceci fut attribué à la brièveté de la période d'essai.

Le progrès des malades, cinquante en tout, traités par la suite à la chloroquine, fut satisfaisant. Un seul ne réagit pas très nettement, en dépit d'un traitement longtemps poursuivi, et trois autres furent soustraits tôt au traitement en raison de leur faible réaction. Aucun effet toxique de quelque importance ne fut remarqué chez les malades traités quotidiennement, durant deux ans, avec 300 mg. de sulphate de chloroquine.

L'essai, bien que ne donnant pas de preuve concluante pour la valeur à long terme de la chloroquine contre l'arthrite rhumatismale, apporte des données suffisantes pour autoriser une investigation plus poussée.

La cloroquina y la artritis reumatoide

SUMARIO

Sesenta y seis enfermos con artritis reumatoide activa fueron asignados al azar en números casi iguales al tratamiento durante 16 semanas sea con cloroquina, sea con comprimidos semejantes pero inertes. Aunque estos dos grupos no fueran perfectamente apareados, no hubo diferencia entre ellos respecto a la duración o la severidad de la enfermedad. Hasta el médico ignoraba cual de los tratamientos sus pacientes recibían. Todos los enfermos recibían también 2,6 gramos de aspirina diaria así como adecuada fisioterapia. Durante la primera parte de la investigación la dosis diaria de cloroquina fué 200 mg., pero luego la dosis fué aumentada a 300 mg. Una base numérica elaborada para una avaluación clínica subjetiva y objetiva, permitió observar que el grupo testigo mejoró un poco, mientras que el grupo tratado con cloroquina manifestó una mejoría significativa aunque no substancial. No se notaron alteraciones en la velocidad de sedimentación eritrocitaria o en las cifras de hemoglobina, atribuyéndose esto a la brevedad del período de investigación.

El progreso de los enfermos, cincuenta en todo, tratados subsiguientemente con cloroquina, fué satisfactorio. Un solo no respondió claramente a pesar de un tramiento prolongado y en tres otros hubo que suspender temprano el tratamiento por falta de respuesta adecuada. No se observaron efectos tóxicos de importancia en enfermos tratados con 300 mg. de sulfato de cloroquina diarios durante 2 años.

La investigación, sin ofrecer pruebas conclusivas acerca del valor de la cloroquina en el tratamiento de plazo largo de la artritis reumatoide, provee sin embargo datos suficientes para justificar estudios ulteriores.

Ann. rheum. Dis. (1956), **15**, 258.

HYDROCORTISONE *TERTIARY*-BUTYLACETATE FOR INTRA-ARTICULAR THERAPY IN RHEUMATIC DISEASES

BY

JACK ZUCKNER, OTAKAR MACHEK, AND ARCH M. AHERN

Section on Arthritis, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Mo.

(RECEIVED FOR PUBLICATION JULY 10, 1956)

In arthritic individuals who have only one or two peripheral joints causing difficulty, it would seem advisable to treat these joints locally by direct intra-articular injection of medication in an effort to decrease the incidence and severity of toxicity associated with systemic therapy. The first very effective anti-rheumatic preparation for intra-articular injection was hydrocortisone acetate (hereafter referred to as hydrocortisone). Hollander, Brown, Jessar, and Brown (1951), Stevenson, Zuckner, and Freyberg (1952), and Kersley and Desmarais (1952) demonstrated a beneficial response in approximately 70 to 80 per cent. of joints so treated with an average duration of improvement 2 to 3 weeks. Recently, Hollander, Brown, Jessar, Udell, Smukler, and Bowie (1955) reported superior results with a derivative of hydrocortisone, hydrocortisone *tertiary*-butylacetate* (hereafter referred to as TBA). The purpose of this article is to report our experiences with the intra-articular administration of TBA in 38 patients, eighteen with rheumatoid arthritis, and twenty with osteo-arthritis.

Material and Method

Hydrocortisone and TBA were supplied for this investigation in the usual saline suspension containing 25 mg./ml.

Routine surgical preparation was used before each injection. In most instances, ethyl chloride was sprayed over the site of injection for local anaesthesia; infrequently, 1 per cent. procaine was administered. If a large quantity of fluid was to be aspirated, a 20-gauge needle was used; for steroid injection only, a 24-gauge needle was satisfactory. All available fluid was aspirated before the injection of the hormone.

The dose of hormone injected varied from 5 mg. into a finger joint to 100 mg. into larger articulations. The interval between injections was usually determined by the patient's subjective response, especially the reduction of pain. Effort was made to maintain at least 50 per cent. decrease of pain and stiffness in the joint treated.

Hydrocortisone and TBA were used alternatively without the patient's knowledge. Evaluation of the comparative effectiveness of these two steroids was made only if there were at least two injections of each into the same joint.

Patients were examined once weekly at first, and later less often in most instances. A composite estimate in percentage of subjective improvement in pain and stiffness, and also an objective evaluation of range of motion, swelling, capsular thickening, tenderness, heat, and degree of synovial fluid in treated joints was recorded.

Altogether 53 joints were treated in 38 patients (Table I). Knee joints were injected in the majority of cases.

TABLE I

DIAGNOSIS OF TREATED JOINTS

Site	Number of Joints	
	Rheumatoid Arthritis	Osteo-Arthritis
Knee	20	25
Shoulder	1	1
Wrist	1	0
Elbow	4	0
Finger	0	1

One individual was under observation for as long as 383 days. Patients with rheumatoid arthritis were followed an average of 116 days, osteo-arthritic patients 111 days (Table II).

TABLE II

DURATION OF OBSERVATION

No. of Days Observed	Number of Joints	
	Rheumatoid Arthritis	Osteo-Arthritis
0– 25	1	4
26– 50	4	0
51–100	8	6
101–200	9	14
201–300	3	3
More than 300	1	0

* Merck and Co. supplied the hormones used in this study.

TABLE III

NUMBER OF INJECTIONS

Injection		Hydrocortisone						TBA				
Dose (mg.)		5	25	37·5	50	100	Total	5	25	50	100	Total
Diagnosis	Rheumatoid Arthritis	0	50	2	6	0	58	0	46	5	2	53
	Osteo-Arthritis	1	48	1	3	3	56	1	50	6	7	64
Total Injections		1	98	3	9	3	114	1	96	11	9	117

The total number of intra-articular injections was 231 (Table III); 114 were hydrocortisone, and 117 TBA. The most frequently administered dose was 25 mg. Twelve 100-mg. injections were given.

Two or more injections each of hydrocortisone and TBA were administered in the same 24 joints for comparative studies; half these joints were rheumatoid, and half osteo-arthritic.

Results

No significant difference between hydrocortisone and TBA could be demonstrated in seventeen of 24 joints in which comparisons were made. Rheumatoid arthritis was present in nine of these articulations and osteo-arthritis in eight. TBA gave better results in five joints and hydrocortisone was superior in two. In no instance was the response to one drug dramatically superior to the other. The immediate improvement and duration of benefit were not significantly greater with either. The average duration of improvement with each drug was 2 to 3 weeks and did not vary with the diagnosis of the treated joint. The results in four rheumatoid and two osteo-arthritic joints were poor with both medications and this form of therapy was discontinued.

Larger doses of TBA in ten joints showed no consistent superiority over smaller doses. Thus, when 100 mg. TBA was compared with 25 mg. TBA in the same articulation, one joint did slightly better on the larger dose, three surprisingly responded more satisfactorily to the smaller amount, and there was no variation in response in three. In one joint, 100 mg. TBA was considered to equal 50 mg. TBA; in two other joints, 50 mg. TBA equalled 25 mg. TBA.

Toxic reactions with TBA were similar to those described with hydrocortisone. An occasional patient complained of increased pain on the evening of an injection, but this was minimal. No infection or systemic toxicity occurred.

Discussion

Hydrocortisone *tertiary*-butylacetate (TBA) is another effective agent for intra-articular injection in rheumatic disorders. When compared with hydrocortisone acetate (hydrocortisone), no significant difference in anti-rheumatic action could be demonstrated. The characteristic responses with hydrocortisone are likewise applicable to TBA. Thus, one cannot predict in advance the degree of improvement that will ensue after injections even in the same articulation. Because of this, it was not considered advisable to compare these preparations unless two injections of each hormone were administered in the same joint.

Approximately 80 per cent. of treated rheumatoid or osteo-arthritic joints derive satisfactory benefit from intra-articular TBA. Duration of improvement is variable, averaging 2 to 3 weeks, but lasting in some instances several months. The optimum dose is 25 mg. for larger joints. Doses up to 100 mg. did not prove more beneficial. Hip joints were not included in this study, but results might be expected to be generally poorer as with hydrocortisone.

Suitable candidates for this form of therapy include patients with involvement of only one or two peripheral joints, and patients with many diseased joints but only one or two causing marked discomfort. When other medications such as steroids and gold salts are contraindicated, or when some of the systemic measures utilized do not adequately control the symptoms, local intra-articular injections should be given to the more affected joints.

Summary

(1) Hydrocortisone *tertiary*-butylacetate gave satisfactory benefit in approximately 80 per cent. of injected rheumatoid and osteo-arthritic joints.

(2) Duration of improvement in the treated joints averaged 2 to 3 weeks.

(3) 25 mg. was the optimum dose, even for large articulations.

(4) No significant difference in anti-rheumatic response was demonstrated between hydrocortisone *tertiary*-butylacetate and hydrocortisone acetate when injected intra-articularly.

REFERENCES

Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., and Brown, C. Y. (1951). *J. Amer. med. Ass.*, **147**, 1629.
——, ——, ——, Udell, L., Smukler, N. M., and Bowie, M. A. (1955). *Ibid.*, **158**, 476.
Kersley, G. D., and Desmarais, M. H. L. (1952). *Lancet*, **2**, 269.
Stevenson, C. R., Zuckner, J., and Freyberg, R. H. (1952). *Annals of the Rheumatic Diseases*, **11**, 112.

Le butylacétate *tertiaire* d'hydrocortisone pour la thérapie intra-articulaire dans les maladies rhumatismales

RÉSUMÉ

(1) Le butylacétate *tertiaire* d'hydrocortisone donna une amélioration satisfaisante dans 80% de cas d'injections dans des articulations rhumatisantes et ostéoarthritiques.

(2) La durée de l'amélioration dans les articulations traitées était en moyenne de deux à trois semaines.

(3) La dose optima était 25 mg., même pour les grosses articulations.

(4) Aucune différence significative dans la réponse antirhumatismale ne fut mise en évidence, entre le butylacétate *tertiaire* d'hydrocortisone et l'acétate d'hydrocortisone par voie intra-articulaire.

El butilacetato *terciario* de hidrocortisona para la terapia intra-articular en las enfermedades reumáticas

SUMARIO

(1) El butilacetato *terciario* de hidrocortisona dió resultados satisfactorios en el 80% de casos de inyecciones en articulaciones reumáticas y osteoartríticas.

(2) La duración de la mejoría en las articulaciones tratadas fué, en promedio, de dos a tres semanas.

(3) La dosis optima fué 25 mg., incluso para las grandes articulaciones.

(4) No se notó diferencia significativa en la respuesta antireumática entre el butilacetato *terciario* de hidrocortisona y el acetato de hidrocortisona por vía oral.

BOOK REVIEWS

Ankylosing Spondylitis. By J. Forestier, F. Jacqueline, and J. Rotes-Querol. 1956. Pp. 374, 145 figs. Thomas, Springfield, Ill.; Blackwell Scientific Publications, Oxford. (81*s.*)

In the United States ankylosing spondylitis and rheumatoid arthritis are usually regarded as varieties of a single disease. In the opinion of the authors of this book the two diseases are distinct clinical entities which should not be confused.

The early symptoms are well described. Pain in the buttock and posterior aspect of the thigh, referred to as the sacro-iliac syndrome, was frequently encountered in the phase of onset in the authors' series of 400 cases. They rightly call attention to the importance of this early symptom. A valuable chapter is devoted to modes of onset and their frequency. It is interesting to note that involvement of the peripheral joints preceded all spinal symptoms in 21 per cent. of cases. The importance of a methodical clinical examination, including measurements of spinal and hip movements, is emphasized. Most rheumatologists would agree with the account of early symptoms and signs given in this book, yet these usually receive less attention than the later manifestations of the disease in current text-books of medicine.

In the chapter on diagnostic problems it is surprising to find no mention of either crippling fluorosis or the sacro-iliac joint changes in traumatic paraplegia. The authors state that iritis is more common in ankylosing spondylitis than in rheumatoid arthritis, and consider that this is contrary to the generally accepted opinion. Certainly in Great Britain, if not in France, it is generally accepted that iritis has a higher incidence in ankylosing spondylitis.

More information could have been given in the chapter on laboratory tests. The observation that the erythrocyte sedimentation rate is normal in one-quarter of the cases in the first year is of interest. The impression is given that anaemia in ankylosing spondylitis is never severe, but this is not so. Information on synovial fluid examination is very scanty.

A detailed account is given of the *x*-ray appearances of the spine and sacro-iliac joints which are encountered as the disease progresses. An attempt is made to correlate sacro-iliac joint changes with the duration of symptoms. A description of the normal *x*-ray appearances of the sacro-iliac joints is welcome. The authors do not consider that oblique views add much to the information obtained from antero-posterior views of the sacro-iliac joints. When changes in the sacro-iliac joints are doubtful they favour tomograms as an aid to diagnosis, and a useful account is given of tomography of the sacro-iliac joints. The authors describe cases in which early bony condensation near the sacro-iliac joints disappears leaving an apparently normal joint space instead of going on to bony ankylosis as is usual. They suggest that this may explain rare cases in which the clinical picture strongly suggests ankylosing spondylitis, but the *x*-ray appearance of the sacro-iliac joints is normal.

The regime of rest and exercise advised in treatment is sound and the details of exercises are helpful. Treatment with gold is considered to be of value, which is contrary to the opinion of authorities in Great Britain and the United States. The combination of gold with butazolidin or "Irgapyrin" in the early stages is advised. No mention is made, however, of the possible risk of combining two drugs each of which has a toxic effect on the bone marrow.

The value and limitations of radiotherapy are fully discussed. Cortisone and ACTH therapy is considered of value in very severe cases, but for the average case it is thought that these drugs do not offer a practical method of treatment.

This book gives a detailed and interesting account of ankylosing spondylitis and is worthy of study by those interested in the rheumatic diseases. C. E. QUIN.

Rhumatologie Clinique. By Pierre P. Ravault and Georges Vignon. 1956. Pp. 604, 180 figs. Masson, Paris. (4,000 *Fr. frs*; £4 4*s.*)

This volume from the Lyons School of Medicine is intended not as a treatise on rheumatology but as a guide to those interested in the practical aspects of the subject. Nevertheless it covers a remarkable amount of ground and the "main" diseases, *e.g.* osteo- and rheumatoid arthritis, ankylosing spondylitis, are described at length in several excellent chapters. The section on scapulo-humeral peri-arthritis is worthy of special praise. Moreover the task of the reader has been eased considerably by the provision of good format, clear pictures, and *x*-ray photographs of superior quality; instead of separate legends, which can be so irksome, a detailed interpretation appears under each photograph. The few blemishes are to be found in the treatment of the "minor" affections which one so frequently encounters in the out-patients department. Thus, a section entitled "Acroparasthésie Douloureuse Nocturne" (p. 510), contains a brilliant description of the menopausal woman who awakes in the early hours of the morning with intense tingling in the fingers and a feeling that they are swollen to twice their normal size. There follows a long discussion on the essentially negative radiological and clinical findings, the thoracic outlet, the sympathetic, etc., and the end of the chapter is reached without the median nerve or the carpal tunnel being mentioned, although Kremer and his colleagues described the syndrome over 3 years ago. In the treatment of "trigger" finger the question of surgery is not even raised.

Continental treatment differs in certain respects from British practice, and more emphasis, for instance, is placed on spas. Also the patient abroad seems to associate radio-activity, in some vague manner, with the treatment of rheumatism—a habit of thought which is not discouraged. In fact, it may be said that, if dreams are the product of experience in the waking hours, the reviewer of continental medical literature is likely to have his slumbers disturbed by visions of petrol-pumps labelled "Fill up here with Thorium-X" and high voltage machines advertising "Emanations without Examinations"; in Great Britain, on the other hand, the public is becoming radiation-conscious, experts are questioning the desirability of certain diagnostic-radiology procedures, and there is even heart-searching over the possibility that a proportion of cases of ankylosing spondylitis treated by deep *x*-rays may develop leukaemia in later years.

The authors have provided an adequate alphabetical index but have deliberately curtailed the bibliography and quoted French references wherever possible; this measure of economy may be not unconnected with the cost of publication in France which, to judge by the price of the volume, is considerably higher than in England.

DAVID PREISKEL.

Collagen Diseases. By John H. Talbott and R. Moleres Ferrandis. 1956. Pp. 232, 30 figs. Grune and Stratton, New York. ($6.50; 45*s*.)

The works of the senior author of this book are well known to all serious students of medicine; few people are better qualified to review the world's literature on the collagen disorders.

The book is well-produced and readable. A total of 540 references are listed at the end of the book under the headings of the five chapters: Systemic lupus erythematosus, Polyarteritis, Dermatomyositis, Systemic scleroderma, and (somewhat surprisingly) Thrombotic thrombocytopenic purpura. The subject matter is well arranged to form a useful book of reference for the student of this group of disorders. There are a few omissions—cranial arteritis is not mentioned in the differential diagnosis of polyarteritis, and scleroedema is only mentioned once with no discussion of its importance in differential diagnosis and no clinical details.

The *x*-ray reproductions and black and white illustrations are clear and demonstrate the relevant details satisfactorily, but the same cannot be said of the sixteen coloured plates appearing on pp. 1–8. The colour of the butterfly rash on the face of a patient with disseminated lupus erythematosus is a very characteristic one, of which the reproduction in Plate I gives quite a false impression; it is clear that these plates have suffered considerably in reproduction. This is, however, perhaps a minor defect in an otherwise well-produced and compact handbook of an intriguing corner in the field of medicine.

F. DUDLEY HART.

Osteo-Arthritis. A Handbook for Patients. 1956. Published by the Empire Rheumatism Council, London. (Free on application to the Secretary, E.R.C., Tavistock House, London, W.C.1.)

This anonymous booklet of twenty pages has been written for the encouragement of the sufferer from osteo-arthritis. It explains in simple but attractive language not only what osteo-arthritis is, but also what it is not. The structure of the joint is explained first and then follows a description of why degenerative changes occur. Fallacies are neatly controverted and misconceptions succinctly removed, as in the following five statements:

> Creaks and clicks in joints do not mean arthritis or rheumatism. It's not what the *x* ray looks like, but how the joint works that counts. Cold and damp may make you feel your aches and pains more, but they don't cause arthritis. Osteo-arthritis isn't due to acid in the joint. Diet doesn't matter unless you are too fat.

In the advice on treatment a nice definition is achieved between the virtue of mobility and the vice of over-activity.

This is a companion booklet to the admirable publication of the Empire Rheumatism Council on *Rheumatoid Arthritis*. It is equally successful and, like its fellow, enjoys the advantage of many humorous line-drawings by Leslie Starke which gaily decorate, although they cannot illuminate, the text. This is a priceless work which freely encourages and consoles the sufferer from osteo-arthritis, and should now be compulsory reading in all rheumatic clinics. It is a model for all those doctors who would educate the patient in his understanding of his disease.

DOUGLAS HUBBLE.

HEBERDEN SOCIETY

Clinical Meeting.—A meeting was held in the London Hospital Medical School on February 24, 1956.

Drs. E. G. L. Bywaters, B. Ansell, and I. Isdale presented a paper on "Prognosis in Still's Disease as compared with Rheumatoid Arthritis".

In a series of over 200 cases of Still's disease seen at Taplow, the prognosis seems to be better than that in adult rheumatoid arthritis. Because of various factors affecting selection, strict comparison can only be made between cases seen early in the course of their disease. In 84 of these, seen within one year of the onset, the functional state compared originally and after 1, 2, 3, and 4 years shows a general improvement; only three patients failed to get better. A comparison was made with 125 adults, also all seen within a year of the onset of their disease, who formed part of the group being followed over a long-term period with the aid of the Nuffield Foundation. Here the results, although better than in adult cases seen after 1 year from onset, were worse than those found in the early childhood group. After dealing with the factors influencing prognosis and other manifestations of childhood disease, Dr. Bywaters detailed the results of a controlled trial of therapy of Still's disease with cortisone *versus* aspirin, which was being conducted under the auspices of the Medical Research Council and Nuffield Foundation Joint Committee, and has since been published (Ansell, Bywaters, and Isdale, 1956).

Ansell, B. M., Bywaters, E. G. L., and Isdale, I. C. (1956). *Brit. med. J.*, 1, 1075.

Dr. M. Keech presented a Paper on "Further electronmicroscopic observations on the transformation of collagen fibrils into 'elastin'."

The morphological response of both "moth-eaten" fibres (collagenase-treated human-skin collagen from different age-groups) and alkali-produced "elastin" (alkali-treated collagen) to various physical, chemical, and enzymatic agents was described. Most of these agents produce a dramatic conversion into "manufactured" elastic networks together with easily identifiable "moth-eaten" fibre conversion structures.

A striking age-difference in the response of collagenase-treated collagen to heat is demonstrated.

It is believed that "moth-eaten" fibres are intermediate structures, midway between collagen and elastin, and are the electron-microscope equivalent of the refractile fibres described by Cruise (1956).

Cruise, A. J. (1956). *Proc. roy. microscop. Soc.* (in the press).

In the clinical demonstration which followed the following cases were shown:

(1) Sir Russell Brain: Cervical Spondylolisthesis with Cord Compression and Paralysis of the Left Diaphragm.
(2) Mr. H. Osmond-Clarke (presented by Mr. G. C. Attenborough): Osteo-arthritis of the Hip located by "Charnley Compression Arthrodesis". This was followed by a discussion on this new operation.
(3) Sir Horace Evans (presented by Dr. J. H. Ross): Polyarthritis, Uveitis, Disseminated Sclerosis, and Sexual Retardation in a Girl aged 17.
(4) Dr. W. S. Tegner: Generalized Osteopetrosis presenting as Osteo-Arthritis of the Knees.
(5) Dr. R. M. Mason: Alkaptonuria with Ochronosis of Spine and Ears, previously diagnosed as Ankylosing Spondylitis.
(6) Dr. J. H. Glyn: Neuropathic Joints and Rheumatoid Arthritis in a Patient suffering from Syringo-Myelia.

Heberden Round.—This was given on June 1 and 2, by Dr. G. D. Kersley, at The Royal United Hospital, Bath. Fifteen clinical cases were shown and discussed.

Two cases had first appeared under the guise of "rheumatism":

(1) An osteoid osteoma of the thoracic spine commencing at the age of 13, undiagnosed for 5 years, and then cured completely by surgery. There had been localized tenderness, severe pain relieved only by massive doses of aspirin, and no other changes until a small area of absorption became visible in the lamina of the 5th thoracic vertebra.

(2) A case of osteoporosis circumscripta in Paget's disease.

Then followed a series of abnormalities of the cervical spine:

(3) Posterior osteophytosis with paraplegia and complete recovery following surgery. Points raised were the short history and good prognosis, the value of trying the Queckenstedt test in full flexion and extension of the neck, and the desirability of doing myelography in this region only when a neurosurgeon was available in case of "contretemps".

(4) Anterior osteophytosis causing the Globus syndrome and (5) marked *x*-ray osteophytosis with minimal symptoms.

(6) A case of subluxation of C,4-5 with diplegia due to rheumatoid changes and marked improvement after traction and the fitting of a collar. Cervical subluxations seen at the Royal National Hospital during the last 10 years were reviewed: seven had been the result of rheumatoid disease, two of which had succumbed; one which had been due to Neisserian infection, had

made a complete recovery; one due to gout; one due to sarcoma.

Other rheumatoid syndromes:

(7) Severe rheumatoid arthritis of the wrists and hands for 20 years with complete absence of pain, marked disorganization, but no neurological lesion.

(8) An "episodic" rheumatoid, who for 9 years had had attacks in the knees only, always occurring at 12-day intervals and lasting 2 days. The sedimentation rate had always been normal, there were no *x*-ray changes except a little osteoporosis, symptoms were only controlled by gold or synovectomy, and typical rheumatoid pathology had twice been demonstrated on biopsy. Intermittent hydrarthritis, palindromic rheumatism, and allergy were discussed.

(9) A case of allergic arthritis resembling rheumatoid arthritis was shown, with cure following removal from the diet of coffee and fish.

Of thirteen cases of rheumatoid arthritis and asthma, the asthma and rheumatoid symptoms had alternated in seven, had seemed to correspond in two, and had had no relationship in four.

Dr. Kersley then took up a previous challenge that rheumatoid arthritis and gout were very rarely associated together, and showed three cases (10, 11, 12) in which both probably coexisted. Of 69 cases of gout, seventeen had also shown definite rheumatoid features; of this seventeen, fourteen were males.

A very severe case of tophaceous gout (13) was then demonstrated, with *x*-ray findings ranging over 10 years. The D.A.T. was negative.

In twenty cases of uncomplicated gout reviewed, the D.A.T. had been normal in every case. In ten of the gout+rheumatoid arthritis group, seven D.A.T.s were positive.

A challenge was then thrown out as to the value of a normal plasma uric acid in excluding a diagnosis of gout, and a case (14) was shown in whom the plasma uric acid had been estimated 57 times, all values being under 6 mg. per cent. In ten out of 55 cases of gout, normal plasma uric acid values had been a common feature before Benemid or large doses of salicylate had been used.

Finally (15) a case showing one of the "collagenoses" was on view for favour of diagnosis.

The following papers were given:

Animal Experiments with Radio-Active Gold, by Dr. M. R. Jeffrey (*Bath*).

Gold is still widely used in treating rheumatoid disease. Very little is known of its distribution or effects within the human body. The radio-isotope ^{195}Au (half-life 185 days) offers the possibility of information on the long-term distribution and excretion of gold. Preliminary results of animal experiments, undertaken before human use is considered, are reported.

Up to one month after injection, the pattern of distribution is similar in healthy rats, guinea-pigs, and rabbits. Up to 30 per cent. of the dose remains at the injection site and the kidneys concentrate much more activity than any other tissue. Roughly one-third of the dose is excreted in a month. When inflammation is produced by the granuloma pouch technique of Selye, gold is more rapidly mobilized, only about 2 per cent. of the dose remaining at the injection site after a month. All tissues contain a larger amount and the rate of excretion is doubled.

Studies of the distribution at longer intervals after injection and of the finer details of distribution, using autoradiography, are proceeding.

***In Vitro* Metabolic Studies of Synovial Membrane,** by Dr. D. P. Page Thomas and Mr. J. T. Dingle (*Bath*).

Synovial tissue from traumatic cases was shown to have a very low oxygen uptake, but a comparatively higher rate of aerobic and anaerobic glycolysis. There was a marked inhibition of glycolysis under aerobic conditions.

Rheumatoid synovia were classified into three types depending upon their proliferative state. All classes showed much greater metabolic activity than the synovia of traumatic aetiology. The metabolic activity of the rheumatoid synovia varied with their proliferative state, the most actively metabolizing tissues being found where the proliferative state was most intense. These rheumatoid synovia had a high degree of aerobic glycolysis. The lower oxidative metabolism displayed by the less proliferative rheumatoid synovia was not thought to be due to a diminution of enzymes or co-factors as the various enzyme systems of the tricarboxylic acid cycle were capable of stimulation by the addition of appropriate substrates. The *in vitro* effect of hydrocortisone at levels within the usual intra-articular therapeutic range was shown to inhibit aerobic glycolysis and oxidate metabolism to a marked degree. The percentage inhibition was greatest where synovial proliferation was most marked.

Excretion of 17-Ketosteroids in Gout, by Dr. E. R. Cook (*Bath*).

The abnormally low 17-ketosteroid output said to occur in gouty patients is being re-investigated by the determination of total and fractionated urinary 17-ketosteroids. The patients selected were free from renal complications to avoid the false low values reported to occur from urines containing protein.

The 17-ketosteroid excretion of nineteen cases of gout, with a mean age of 53 ± 10 years was $10 \cdot 9 \pm 3 \cdot 7$ mg./24 hrs. Chromatographic analysis of the ketosteroids from fourteen of these patients with a mean age of 49 years showed the usual wide variations in pattern between individuals, the mean values being dehydroisoandrosterone 21 per cent. (range 7–44 per cent.), androsterone 33 per cent. (range 15–44), etiocholanolone 37 per cent. (range 20–57), and 11-oxy-17-ketosteroids 8 per cent. (range 5–13). The androsterone etiocholanolone ratio was 0·9 (range 0·4–2·0).

These figures do not suggest an abnormal 17-ketosteroid excretion in gout, but it must be emphasized that this is a preliminary account of work which is not yet complete.

Peripheral Vascular Studies in Early Rheumatoid Arthritis, by Dr. J. H. Peacock (*Bristol*).

Eleven cases of early generalized rheumatoid arthritis were investigated. Arteriograms performed by puncture of the brachial artery showed no evidence of arterial obstruction in the digital blood vessels. Peripheral nerve blocks of the ulnar, median, and radial nerves confirmed the ability of the blood vessels of the hands to undergo full vasodilatation. Skin temperature studies of the fingers and toes were performed simultaneously with hand and forearm blood flows at a constant room temperature of $20 \pm 0{\cdot}5°$ C. The hand blood flows were measured in a water-filled thermostatically controlled venous occlusion plethysmograph through an entire local temperature range of 18–42° C. The patterns of blood flow obtained were compared with normal standard controls, Raynaud's disease, and acrocyanosis.

The effects of aspirin, intravenous hydrocortisone, phenyl-butazone, and a peripheral vaso-dilator ("Dibenziline") were compared. The degree of vasodilatation induced and improvement of clinical symptoms that resulted were tabulated.

The hand blood flows in five of eleven cases were found to be much higher than those obtained in normal controls. Two cases only were found to have a degree of peripheral vascular ischaemia normally seen in Raynaud's disease. In four cases the blood flows were in the normal or lower normal range.

Vasodilatation induced by the use of Dibenziline was not found to be effective in relieving the symptoms and signs of the rheumatic process.

In some cases a discrepancy between the skin temperatures and blood flows was observed. As the forearm blood flows were found to be in the normal range and no inflammatory process was present in the joints of the hands when the observations were made, this discrepancy appeared to be due to the presence of an arteriovenous shunt. It appeared possible that the relationship normally seen between blood flow and skin temperatures may not apply in this particular condition —further studies are proceeding.

It was seen that the pattern of blood flow in rheumatoid arthritis is infinitely variable, non-specific in character, and possibly linked to stages in the metabolic or endocrine changes associated with the disease process. The sympathetic nervous system is not primarily involved in this condition.

Functional Focus of Human Mechanics and its Significance in Arthritis, by Mr. Norman Capener (*Exeter*).

In dealing with the joints situated around the centre of gravity within the pelvis of the standing person, the speaker developed the theme of Saunders, Inman, and Eberhart (1953) upon the determinants of normal human gait. These authors had shown how the control of the centre of gravity in its passage through space, was economically effected by the rotation and tilting of the pelvis aided by the movements of the hip and knee joints. The speaker dwelt upon the associated movements of the lumbar spine and emphasized the effects of the contrary thrusts exerted from below against the thrusts exerted from above in all dynamic activities of freely-standing people, as in walking, running, and, in particular, with the association of swinging movements of the arms, as in labourers, or in sportsmen such as cricketers and golfers. These thrusts were materially altered by disease or by fixation of joints. Human body mechanics was dominated by the compelling necessity of maintaining the centre of gravity in equilibrium. We should think more of this and of the complexity of the associated joint movement and muscular control, and less of the simpler problems of static weight bearing. Furthermore we should cease to think of the clinical problems of the lumbo-sacral and hip joints as single entities. These joints comprised a compound articulation, limitation of function in one element of which was bound sooner or later to affect adversely the function in each of the other elements. The paper was illustrated by drawings after Leonardo da Vinci, from newspaper photographs of contemporary sports contests, and from the author's own work upon the lumbo-sacral spine and hip joints, together with an articulated model in metal.

Saunders, J. B. de C. M., Inman, V. T., and Eberhart, H. D. (1953). *J. Bone Jt Surg.*, 35A, 543.

The Antigenicity of Synovial Tissue, by Drs. D. G. Scott and A. G. S. Hill (*Stoke-Mandeville, Bucks*).

The immuno-histological method of Coons was used to study the distribution of antigenically active components of human synovial membrane and of human glomeruli.

Globulin fractions prepared from the sera of rabbits immunised with isolated human renal glomeruli or with human synovial membrane were conjugated with fluorescein. Unfixed sections of healthy human organs and tissues were examined under the fluorescence microscope after exposure to one or other of the conjugates. In each case the resulting green fluorescence was shown to be specific by its failure to appear if the section had been pre-treated with unlabelled antiserum before "staining" with the corresponding conjugate. The distribution of specific fluorescence produced by the one conjugate was compared with that produced by the other. Cross inhibition experiments in which sections were pre-treated with antiglomerulus globulin before exposure to conjugated antisynovia globulin (and *vice versa*) were performed to compare the antibody content of the two antisera.

The results of the experiments indicated that reticulin and basement membrane are antigenically distinct. The renal glomerulus was shown to possess both antigens while only the reticulin antigen was demonstrated in the synovial membrane and only the basement membrane antigen was found in the media of muscular arteries.

It was suggested that a study of the distribution of reticulin and basement membrane throughout the body might help towards an understanding of the significance of the sites of the lesions in the diffuse mesenchymal diseases.

Laboratory Tests in the Control of Steroid Therapy in Rheumatoid Arthritis, by Dr. J. H. Glyn (*London*).

The absence of and the need for objective criteria for controlling steroid therapy was stressed.

Certain laboratory estimations were applied to this problem in eight cases of rheumatoid arthritis undergoing treatment with cortisone or hydrocortisone. Serial estimations were performed throughout treatment and compared to this clinical finding.

The tests were chosen for their simplicity so that they might be used continually if they proved useful. Most of them were non-specific "acute-phase" serological reactions.

It was hoped that they would also prove helpful in distinguishing a true remission of the disease from cortisone suppression, also in the problem of case selection and the "screening" of new "anti-rheumatic" drugs.

The results indicated that the tests could broadly be divided into two groups of which the serum hexosamine, the Winzler mucoproteins, and the total protein-bound polysaccharides are the most obstinate and therefore the most reliable indices of underlying disease activity. By contrast, tests such as the "C-reactive protein" are excessively sensitive, but seem to reflect the day-to-day variations more accurately and rapidly.

In general these tests did not prove sufficiently reliable to recommend them for routine clinical application.

The relationship of the hexosamine, mucoproteins, and polysaccharides to each other and to the primary disorder of the ground substance was discussed in some detail.

Sensitized Sheep Cell Test in Rheumatoid Arthritis, by Drs. Rowland Alexander and Lynda Roy (*Edinburgh*).

The Coons fluorescent-protein technique was used in an attempt to demonstrate transfer of protein from rheumatoid serum to sensitized sheep erythrocytes. The experiments were unsuccessful, but examination of other haemagglutinating systems showed that erythrocytes agglutinated by fluorescein-conjugated antibody were rendered fluorescent only when the antibody had been prepared against whole erythrocytes.

It was suggested that the factor in rheumatoid serum responsible for enhanced agglutination of sensitized sheep erythrocytes was active in very small amounts, and preliminary results of experiments with fractions of serum prepared in the ultracentrifuge supported this contention.

FUTURE ARRANGEMENTS

Clinical Meeting, on October 19, at 4.30 p.m., at the Wellcome Foundation.

Heberden Oration, 1955, on "Research and the Rheumatic Diseases", by Dr. Walter Bauer, on October 19, at 8.30 p.m., at the Royal Society of Medicine.

Heberden Oration, 1956, on "The Connective Tissue System", by Prof. R. E. Tunbridge, on December 14, at 5 p.m., at the Wellcome Foundation.

Annual Dinner, 1956, on December 14, at 7.45 for 8 p.m., at the Apothecaries Hall, Blackfriars Lane, Queen Victoria Street, E.C.1.

Annual General Meeting, 1956, on December 15, at 9.30 a.m. at the Wellcome Foundation.

Clinical Meeting, on December 15, at 10 a.m. as above.

AMERICAN RHEUMATISM ASSOCIATION

The Annual Meeting was held on June 8 and 9, 1956, at Chicago, Ill., under the presidency of Dr. Charles L. Short. The scientific sessions included a panel discussion on Gout, and also one on "A Teaching Collection of Lantern Slides illustrating the Pathology of Arthritis and Rheumatism", the work of a Sub-committee of the Arthritis and Rheumatism Foundation. The A.R.A. Committee on Diagnostic Criteria presented a Report on Criteria for Rheumatoid Arthritis. Part of the programme was arranged in collaboration with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. A full account of the proceedings with summaries of the papers and discussions thereon will be published in the December issue of the *Annals*.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

IX INTERNATIONAL CONGRESS, TORONTO, 1957

The Ninth International Congress on Rheumatic Diseases will be held at Toronto, Ontario, Canada, from June 23 to 28, 1957. This quadrennial function of La Ligue Internationale contre le Rhumatisme will be held under the auspices of the Canadian Rheumatism Association.

The Programme Committee invites contributions to the scientific programme of the Congress and is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases.

Those offering papers for consideration should submit a 200- to 300-word abstract, not later than January 1, 1957, in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, it will be helpful, though not essential, if it can be accompanied by an English translation.

All correspondence should be directed to:

The Ninth International Congress on Rheumatic Diseases,
Post Office Box 237,
Terminal "A",
Toronto, Ontario, Canada.

Le Neuvième Congrès International sur les Maladies Rhumatismales aura lieu à l'hôtel Royal York, Toronto, Ontario, Canada, du 23 au 28 juin 1957.

Toute correspondance doit être adressée à The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A" Toronto, Ontario, Canada.

Der Neunte Internationale Kongress fuer die Erforchung rheumatischer Krankheiten wird im Royal York Hotel in Toronto, Ontario, Canada, vom 23. bis zum 28. Juni 1957 stattfinden.

Wir bitten, jede Korrespondenz an folgende Anschrift zu senden The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A", Toronto, Ontario, Canada.

El IX Congreso Internacional de Enfermedades Reumaticas tendra lugar en el Hotel Royal York de Toronto, Ontario, Canada, del 23 al 28 de Junio de 1957.

Toda la correspondencia debera ser dirigida a The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A", Toronto, Ontario, Canada.

CANADIAN RHEUMATISM ASSOCIATION
SOCIÉTÉ CANADIENNE DE RHUMATOLOGIE

The Annual Meeting of the Canadian Rheumatism Association was held in Quebec City on June 14 and 15, 1956. La Société du Rhumatisme de Québec acted as host at the social events and demonstrated the charm of our French Canadian culture and the beauty of our oldest city to the English-speaking members. An official French name for the Canadian Rheumatism Association was adopted, *viz.* "La Société Canadienne de Rhumatologie". Thirty new members were elected, bringing the total membership to 144. Mr. Edward Dunlop and Mr. B. H. Rieger were made honorary members for their work with the Canadian Arthritis and Rheumatism Society and the Congress Committee.

The forthcoming Ninth International Congress on Rheumatic Diseases will be held in Toronto, Canada, on June 23 to 28, 1957. The Canadian Rheumatism Association will be host to this event and it is hoped that the Canadian bilingual culture will make all visitors welcome. The plans and arrangements are under a Congress Committee whose chairman is Dr. D. C. Graham. The plans outlined at this meeting suggest that everything will be well arranged.

The following Executive was elected for 1956-57:

President: Dr. A. A. Fletcher, Medical Arts Bldg., Toronto, Ont.

Past President: Dr. H. G. Kelly, Kingston General Hospital, Kingston, Ont.

First Vice-President: Dr. Roland Dussault, 847 Rue Cherrier, Montreal, P.Q.

Second Vice-President: Dr. A. W. Bagnall, 3195 Granville Street, Vancouver, B.C.
Secretary-Treasurer: Dr. J. B. Frain, Winnipeg Clinic, Winnipeg, Man.
Representing Council: Dr. M. A. Ogryzlo, Toronto General Hospital, Toronto, Ont.
Dr. de Guise Vaillancourt, Hôtel Dieu, Montreal 18.

Scientific Sessions.—These were held under the chairmanship of the 1955-56 President, Dr. H. G. Kelly, assisted by Dr. Jean Rousseau of Quebec and Dr. de Guise Vaillancourt, the Programme Chairman. Abstracts of the papers presented are printed below:

Vertebral Lipping. By IAN MACNAB (*Toronto*): Four main types of vertebral lipping had been recognized:

Traction spur projecting horizontally from the vertebral body;
Claw lip;
Cap spondylophyte;
Bubble spondylophyte and confluent spondylophytosis.

The term spondylophyte had been used to cover all forms of vertebral lipping. In order to assess the clinical significance of these various forms of spondylophytes, their pathogenesis was studied. The traction spur was found to be associated with a collapsing disk. Cap spondylophytes were formed by metaplasia of the outer fibres of the anulus, and bubble spondylophytes were invariably found in association with tears of the posterior fibres of the anulus.

It was felt that a small traction spur was indicative of a spinal segment that might be the source of pain, especially if this were an isolated finding and especially if it were confirmed by abnormal movements of the flexion extension *x* rays. The claw spondylophyte when small was also associated with an unstable segment but when large was generally indicative of a collapsed and stable segment which was unlikely to be the source of pain. Confluent spondylophytosis was invariably associated with complete bony ankylosis of the associated segment and therefore this segment could not be giving rise to pain. The significance of the cap spondylophyte lay chiefly in its recognition. It was important to differentiate this type of vertebral lipping from fractures of vertebral lips which it simulated.

***Prevention and Correction of Deformity of the Knee in Arthritis.** By ROGER GARIÉPY (*Montreal*): Prevention of flexion contracture of the knee must be initiated very early in the course of an arthritic inflammation; failure to do so induced a deformity which may be permanent. At the stage of the irreversible synovitis, correction of flexion contraction might be achieved by simple manipulations done repeatedly without effort so as to avoid articular injury. Synovectomy might have to be considered in order to improve the mechanical function of the joint. Forceful straightening of the knee under anesthesia might often give good results provided mobilization of the involved joint was resumed soon afterwards. Should ankylosis be marked, a correction of the flexion by osteotomy involving the condyles of the tibia was preferable to a posterior capsulectomy or a supracondylar osteotomy.

* Speaker unable to attend because of family tragedy. Paper not read.

Distribution of Serum Uric Acid and Some Observations on the Activity of Uricase. By JEFFREY E. MORRIS (*Winnipeg*): Serum and serum ultrafiltrate were subjected to electrophoresis on filter paper using a borate buffer. Uric acid was identified as a blue colour by spraying the strips with modified Folin's reagents. With serum two zones were identifiable as free uric acid and albumin-bound uric acid. Serum ultrafiltrate provided a single band corresponding with free uric acid. The concentration of uric acid in serum ultrafiltrate was less than that of the parent serum, the difference being related to the serum albumin concentration in normals and in patients with various diseases.

The activity of uricase powder prepared from ox kidney was investigated on substrates of serum, serum ultrafiltrate and standard solutions of uric acid. Observations of the rates at which uric acid chromogen disappeared from these substrates during their incubation with uricase gave rise to the speculation of the presence of an activator for uricase in serum and serum ultrafiltrate. Further experiments indicated that a heat-stable ultrafiltrate activator existed in serum; it could be absorbed from serum by activated alumina and removed from serum ultrafiltrate by passage through an anion-exchange resin.

Nature and Origin of Fibrinoid in Subcutaneous Nodules of Rheumatic Fever and Rheumatoid Arthritis. By HENRY Z. MOVAT and ROBERT H. MORE (*Kingston, Ont.*): The terms "fibrinoid degeneration of connective tissue" and "fibrinoid substance" were introduced in 1880 by Neumann. The nature and origin of this substance and the process of its formation had puzzled pathologists for the past 75 years, but more especially since Klinge's studies of rheumatic diseases in the early 1930s, and those of Klemperer and his co-workers some 15 years ago. Klemperer, Pollack, and Baehr introduced the term "collagen disease" to cover a group of conditions characterized by alteration of connective tissue and by the presence of fibrinoid.

Various investigators had in turn postulated theories on the origin of fibrinoid from collagen, or fibrin, or ground substance.

The morphological, tinctorial, and histochemical properties of fibrinoid from nine rheumatic and 21 rheumatoid nodules were studied.

In most cases, but particularly in early nodules, fine threads, meshes, and strands of fibrin could be demonstrated which conglomerated to form masses showing all the characteristics of fibrinoid. The latter had been defined as an acidophilic, homogenous, and refractile material giving staining reactions identical to fibrin.

It was demonstrated that haematoxylinophilia and Feulgen positivity were not only properties of fibrinoid in disseminated lupus erythematosus, but also occurred at times in rheumatoid and rheumatic subcutaneous nodules.

Histochemically tyrosine, tryptophane, cystine, and cysteine were present in fibrinoid from both types of nodules. These animo acids were present in serum proteins but absent or in low concentration in collagen. Incubation of tissue with hyaluronidase altered the specific acid mucopolysaccharide staining material but not the fibrinoid. Collagenase digested collagen but left fibrinoid unaltered. Trypsin resulted in the digestion of fibrinoid but not of collagen. Fibrinolysin led to the digestion of fibrinoid in frozen substituted tissue. These findings provided evidence for the almost certain origin of fibrinoid in rheumatic and rheumatoid nodules from fibrin.

Similar findings were also obtained in fibrinoid in other collagen diseases and in fibrinoid produced experimentally.

Antistreptolysin-O Titres in Normal Young Adults and in Disease. By MAURICE SAINT-MARTIN (*Montreal*): A comparative study was presented of antistreptolysin-O serum-levels in five groups of individuals:

(*a*) normal young adults;
(*b*) patients with active rheumatic fever;
(*c*) patients with inactive rheumatic fever;
(*d*) patients with rheumatoid arthritis;
(*e*) patients with miscellaneous diseases accompanied by joint or extremity pain.

Since these levels in a given population were dependent on the frequency of its past streptococcal infections, a survey of normal adults was initiated to indicate what values could be considered as high or low. A low value was arbitrarily established at 50 units or less since 56·6 per cent. had such a titre. A high value was found to be 250 units or more with only 2·2 per cent. of the population included. In active rheumatic fever, 76 per cent. had high values, whereas only one case had a titre of 50 units. Levels somewhat higher than normal were found in inactive rheumatic fever. Values in rheumatoid arthritis and miscellaneous diseases were very similar to those in normal subjects. Mean titres were 665 units for active rheumatic fever, 130 units for inactive rheumatic fever, and 78 units for normal subjects.

Two general patterns were observed in the evolution of rheumatic fever: one, less frequent, where a gradual decrease in titre accompanied clinical recovery, and, another, where the titre remained elevated for many months in spite of clinical recovery. In conclusion, since no single diagnostic test for the presence of active rheumatic fever had been established to date, the determination of antistreptolysin-O titre was a useful procedure in the differentiation of rheumatic fever from other types of arthritis. A low value might be regarded as an important exclusion test, and a high value, although of lesser significance, should be critically appraised before excluding active rheumatic fever.

Observations on Conjugated and Unconjugated Steroids in Human Blood. By MARVIN DARRACH (*Vancouver*): The free and conjugated adrenal steroid fractions of peripheral plasma from twelve normal human males were studied by paper chromatographic methods. The effect of ACTH on blood adrenal steroids in normal and arthritic patients was discussed. A survey of present concepts of adrenal steroid metabolism in the human was related to the rheumatic diseases.

Stress and the Rheumatic Diseases. By GÄÉTAN JASMIN, PIERRE BOIS, and HANS SELYE (*Montreal*): After a brief definition of the meaning of "stress" in its medical connotations, the authors outlined the role of the pituitary-adreno-cortical system in combating the damage produced by various stressor agents. Special emphasis was laid upon ACTH, STH, cortisone, and aldosterone in the production and inhibition of inflammatory reactions in general.

The scientific analysis of the pathogenesis of inflammatory disease depended largely upon appropriate test objects, which permitted a quantitative appraisal of inflammation. Among these tests the "granuloma-pouch" technique, topical irritation arthritis, experimental polyarthritis, and the more diffuse collagen diseases (periarteritis, myocarditis, renal lesions, etc.) induced by overdosage with mineralocorticoids, received special attention.

The available data concerning hormonal factors in the pathogenesis of diseases in man (particularly rheumatic diseases) was surveyed on the basis of hormone determinations in blood and urine.

The observations were interpreted as indicating that stress in general and the pituitary-adrenal system in particular played important parts in the pathogenesis of rheumatic diseases and many other maladies.

Serum Mucoproteins and Electrophoretic Patterns in Rheumatic Diseases. By KENNETH R. MACKENZIE, LOUIS G. JOHNSON, and COOPER H. STACEY (*Montreal*): The nature of the serum mucoproteins was briefly discussed. The level of the serum mucoproteins, using the biuret reaction after precipitation with perchloric and phosphotungstic acids, was measured in four hundred cases of rheumatic disease and these levels were correlated with the nature and activity of the disease process. The serum mucoproteins in an unselected group of 150 cases of rheumatoid arthritis consistently tended to be elevated above the normal and might reach a level in excess of 400 mg. per cent. These values were also elevated in other forms of inflammatory joint disease. The serum mucoprotein levels might increase before clinical exacerbation became evident and return towards normal in association with clinical improvement. It was felt that serial observations of this serum component were of value in following the course of the disease. In osteo-arthritis the levels fell within the normal range unless complicating factors coexisted. Changes in the serum mucoprotein levels during therapy were demonstrated.

Since it was demonstrated that the serum muco-

proteins migrated with the alpha globulins in an electrophoretic field, the electrophoretic pattern of the serum proteins was determined in 57 unselected cases of rheumatoid arthritis. Consistent, but non-specific changes were observed in these patterns during active phases of the disease process. These changes were characterized by a lowering of the serum albumin and an elevation of the alpha 2 and gamma globulins. Changes associated with steroid therapy and the remissions and exacerbations of the disease were demonstrated.

Interrelationship of Various Tests for the "Specific" Rheumatoid Arthritis Factor. By RONALD W. LAMONT-HAVERS (*New York*): Various means had been developed to demonstrate the "specific" factor in rheumatoid arthritis. These included the use of group-A haemolytic streptococci, sheep erythrocytes coated with specific rabbit anti-sera, tannic-acid-treated sheep erythrocytes coated with F 11 fraction of human globulin, latex particles coated with human gamma globulin, and the "neutralization" technique as a precipitin reaction.

The possible common reaction involved in these phenomena, and some ideas on pathogenesis and on the relationship of lupus erythematosus disseminatus to these reactions were discussed.

Case of Metabolic Bone Disease. By ROGER DEMERS, JACQUES DUQUETTE, J. B. GAGNON, and MARC FRANCOEUR (*Montreal*): A 54-year-old married female, in good health until 1951, developed marked myalgia involving mainly the limbs but with no real arthralgia. The myalgias were associated with considerable weakness. She had been bed-ridden for the past 4 years and muscular atrophy had since been progressive. Under cortisone therapy she developed oedema.

Her family physician had given her an average daily dose of 300,000 units of vitamin D to overcome osteoporosis. After 3 months of this therapy, she developed symptoms of vitamin D intoxication. Nodules containing calcium phosphates and urates appeared in the soft tissues of the hands, neck, and shoulder regions.

When admitted to hospital in December, 1955, she was rather drowsy and renal insufficiency was prominent. Extensive metabolic studies, photographs of the nodules, *x*-ray films of the bones, and biopsy reports with slides were presented.

The following suggestions were made:

(1) Primary or secondary hyperparathyroidism with renal insufficiency?
(2) Renal rickets in an adult?
(3) Vitamin D intoxication with metastatic deposition of calcium phosphates and urates in the soft tissues?

Use of Hydrocortisone in Treatment of Painful Shoulder (film). By ARTHUR W. BAGNALL (*Vancouver*): To achieve good results from hydrocortisone injection in the painful shoulder, a special technique must be employed recognizing the following facts:

(1) The inflammation was usually in the soft tissues outside the shoulder joint itself—injection of hydrocortisone into the joint cavity was too often useless.
(2) The most frequent site of inflammation was the subacromial bursa which did not communicate with the shoulder joint.
(3) Almost as frequently involved, either alone, or with the subacromial bursa, was the tendon sheath of the long head of the biceps muscle. Normally, this sheath communicated with the shoulder joint but it was easily shut off by inflammatory adhesions from the shoulder joint.
(4) Other foci of inflammation might be present in the "cuff" of the shoulder, but were much less frequent.
(5) Because of these anatomical variations in the site(s) of inflammation, to ensure good results from hydrocortisone injection, it was necessary to have an accurate "indicator" of whether the injected hydrocortisone had been brought into contact with all the inflammatory foci. Procaine mixed intimately with the hydrocortisone served admirably as such an indicator. At the end of the injection, there should be no further pain on movement of the shoulder.
(6) Tenderness to light palpation over the biceps groove indicated that it was inflamed and it was therefore infiltrated first with the "indicator" mixture. After this, if there was still pain on movement or if the biceps groove was tender, the subacromial bursa was infiltrated and the adjacent capsule explored for tender spots. Non-inflamed structures around the shoulder joint were not painful when needled: thus, the mixture should be injected when painful spots were encountered by the tip of the exploring needle. Occasionally, it was also necessary to infiltrate the inferior cul-de-sac (from behind).
(7) 1 ml. hydrocortisone to 3 ml. 1 per cent. procaine was used for the "treatment-indicator" mixture.
(8) Pain reactions to the needling were not uncommon. They did not prevent an eventual good result but should be anticipated by arranging a small supply of a potent anodyne.

Hypersensitivity Reactions to Cortisone and Its Analogues. By ARTHUR W. BAGNALL (*Vancouver*): Cortisone and its analogues were very useful in the treatment of allergic disorders. However, on rare occasions they themselves might act as foreign-body allergens. Urticaria and angio-oedema had been seen, and even fatal anaphylactic shock had been reported in two cases of asthma when oral cortisone was resumed after an interval of 5 days.

In 1951, the author had published a report on "Paradoxical Behaviour of the Erythrocyte Sedimentation Rate in (intramuscular) Cortisone Therapy". The significance of this was still not clear but might be related to the Arthus phenomenon.

In "non-traumatic" intra-articular injections, one might expect an immediate reaction to the injection of hydrocortisone, or prednisolone in about one in a hundred injections. There was no obvious explanation for this. It might happen with the first injection, and, on the other hand, further injections might be free of this reaction. In some, the pain reaction became worse with each injection, suggesting the pattern of the Arthus phenomenon. This was not the rule and the cause of these local reactions remained obscure.

While a "serum-sickness pattern" had not been reported in the literature to date, two patients had been observed with delayed "serum-sickness pattern", occurring 5 and 10 days after an acute severe immediate local reaction to an intra-articular injection of hydrocortisone acetate in one, and of prednisolone acetate in the other. Both responded satisfactorily, and lastingly, to a short course of oral steroid therapy—cortisone being used in the first instance, and prednisone in the second. In neither was there a past history of allergy.

Local adverse hyper-reactions to hydrocortisone and prednisolone, and more serious reaction patterns, such as "serum-sickness" and shock, were so rare as not to contraindicate the use of these valuable therapeutic adjuncts. Nevertheless, it seemed advisable to call attention to the occurrence of these reactions and to the efficacy of "fighting fire with fire" in their treatment.

Rehabilitation Centre and Rheumatic Diseases. By HAROLD S. ROBINSON (*Vancouver*): A group of 125 rheumatic patients had been treated in the Canadian Arthritis and Rheumatism Society Rehabilitation Centre in Vancouver over a 5-year period. 124 of these patients had been followed by one or more members of the rehabilitation team to the present time.

The team's approach to treatment and the means of follow-up support were discussed briefly. Comment was made on the pitfalls of assessment and rehabilitation treatment in rheumatic states.

The pattern of improvement in the socio-economic sphere was demonstrated.

Stress was laid on the value of a period of intensive treatment in a medical treatment centre where the patient was orientated to his disease, its treatment, and his potentialities. The value of continued follow-up support was implied in the results of the follow-up study.

Rheumatic Manifestations in Hodgkin's Disease, Leukaemia, and Allied Conditions. By EDMOND PAQUET and JEAN-MARIE DELÂGE (*Quebec*): Osteo-arthralgic symptoms, especially vertebral ones, were prominent among the many and varied manifestations of Hodgkin's disease and the leukaemias. In the event of an obscure arthralgia, one should consider the possibility of one of these conditions as being the cause of the ill-defined joint pain.

The frequency of rheumatic pain as an early symptom of Hodgkin's disease or of one of the leukaemias was pointed out; it was shown that arthralgia is a symptom not infrequently encountered during the evolution of these conditions.

Rheumatic pain having been defined, a review was made of several hospital records of patients with Hodgkin's disease, lympho- and reticulosarcomata, acute or chronic leukaemias, and multiple myeloma. The diagnoses were established on clinical data confirmed by anatomo-pathological procedures: biopsy, bone marrow aspiration, or autopsy.

There was no constant correlation between pain manifestations and bone lesions seen in *x* rays. In Hodgkin's disease, the spine, particularly the lumbar segment, was often involved. Involvement of the lumbar segment of the spine or of the sacro-iliac joints almost always induced back pain with or without radiation to the lower extremities.

Osteo-articular manifestations were more frequent in the acute leukaemias of childhood than in any other varieties of leukaemia and often simulated either acute rheumatic fever or Still's disease (juvenile rheumatoid arthritis).

Finally, multiple myeloma might so very well suggest one of the arthropathies that one had to consider this possibility when confronted with an adult patient suffering from an obscure, painful bone pathology. Rheumatic pain was among the most frequent manifestations of multiple myeloma and might be the only clinical manifestation of the disease.

Marie-Strümpell Spondylitis with Rheumatoid Nodules. By HUGH A. SMYTHE (*Toronto*): A great body of evidence had been accumulated which indicated that ankylosing spondylitis, with or without peripheral joint involvement, was an entity distinct from rheumatoid arthritis. Recent observations on heredity, on serological reactions, and on cardiac complications reinforced these views. Proved rheumatoid nodules had never been reported in association with sure spondylitis. Occasional references to the presence of nodules in association with spondylitis and peripheral arthritis were to be found, but case reports and studies of incidence were few.

In a group of over 500 spondylitics investigated in the Arthritis Service at Sunnybrook Hospital, there had been only one with rheumatoid nodules. This case was presented in detail.

Multiple Myeloma: Presenting Symptoms and Course. By JOHN R. MARTIN (*Montreal*): A delay in the diagnosis of multiple myeloma often occurred because of the wide variation in the presenting picture and the fact that it might mimic many other more commonly diagnosed illnesses.

Records of patients with this disease from the Montreal General Hospital, Queen Mary Veterans Hospital, and Royal Victoria Hospital were reviewed with respect to the initial symptoms and the clinical and laboratory findings. The complications and the course of the disease in the patients in this series were also noted.

Some Aspects of Infectious Arthritis. By SIMON DWORKIN, LOUIS G. JOHNSON, and KENNETH R. MACKENZIE (*Montreal*): This report dealt with a group of nineteen male patients whose illness was characterized by two features: recurrent episodes of polyarthritis and a history of gonorrheal infection. In only three cases was an original Neisserian infection proved; in all the others the history of urethritis was clear enough to justify an assumption of such an infection. In two cases out of nineteen, the first attack of arthritis supervened during or shortly after the acute infection; in the rest the joint disease occurred much later, after clinical subsidence of the urethritis.

With respect to clinical course, there was great variation in the degree of articular involvement, as well as in the frequency of attacks. The duration of any one attack varied, but was apt to be rather long.

In order of frequency the joints involved were hands, wrists, feet, knees, and ankles, shoulders, lower back. There were the usual signs of acute inflammation both on the clinical and laboratory side. However in some instances the sedimentation rate and mucoproteins were normal. The ultimate effects in regard to deformity and disability did not seem to be as grave as in cases of equivalent duration or intensity that would be diagnosed as rheumatoid arthritis.

These cases proved very refractory to treatment, whether by a succession of antibiotics, or induced hyperpyrexia, or cortisone. Rest and physiotherapy seemed to be as useful as any of the modalities mentioned.

It seemed reasonable to regard the arthritis described as a sequel to an original gonorrheal infection, although definite proof was often lacking. The main question posed by these and similar observations elsewhere was whether the present method of treating acute presumable or proved gonorrheal infection was adequate, or whether it should be supplemented with follow-up therapy at intervals.

Psychological Factor in Rheumatoid Arthritis. By ALBERT W. GROKOEST (*New York*): A review of the current views on the psychological factor in rheumatoid arthritis was followed by an effort to show that the stress or stimulus, whether infectious, traumatic, or emotional, is non-specific. No central nervous system influence on the peripheral inflammatory lesion of rheumatoid arthritis had yet been demonstrated. With the non-specificity of the stress, a neuro-humeral link was missing in the concept of rheumatoid arthritis as a psychosomatic disease.

Ann. rheum. Dis. (1956), **15**, 273.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Application of the Antistreptolysin-O Titre in the Evaluation of Joint Pain and in the Diagnosis of Rheumatic Fever. ROY, S. B., STURGIS, G. P., and MASSELL, B. F. (1956). *New Engl. J. Med.*, **254**, 95. 7 figs, 16 refs.

The importance of joint pain as a manifestation of rheumatic fever was evaluated in 648 consecutive patients under the age of 17 admitted to the House of the Good Samaritan (Harvard Medical School), Boston, between 1943 and 1948; cases of chorea were excluded from the study. On the criteria adopted (objective signs in two or more joints) significant arthritis was present in 50 per cent. of the patients, and of these joint pain was the presenting symptom in 94 per cent., while cardiac involvement occurred in 50 per cent.

The distribution of the antistreptolysin-O titres was studied in each of four clinical groups in order to determine its value in differentiating the joint pain due to rheumatic fever from that due to other diseases. The patients with rheumatic fever were divided into two groups:

(1) 208 patients with definite rheumatic carditis;

(2) 227 patients with definite rheumatic fever and arthritis.

In these two groups the antistreptolysin-O titres showed a similar distribution, namely, 400 units or more in 82 per cent. of Group 1 and in 85 per cent. of Group 2, and 159 units or less in 3 and 1·8 per cent. respectively.

(3) 75 cases of juvenile rheumatoid arthritis. The titre was 400 units or more in 28 per cent. and 159 units or less in 56 per cent.

(4) 92 patients with miscellaneous diseases of which joint pain was a prominent feature, showed a titre of 400 units or more in 8 per cent. and one of 159 units or less in 59·8 per cent.

It is concluded that joint pain is a frequent, early, and important manifestation of rheumatic fever, and that, while a high antistreptolysin-O titre is consistent with, but not diagnostic of, rheumatic fever, a very low titre may be regarded as excluding active rheumatic fever. The authors add that the height of the antistreptolysin-O titre affords no help in the prediction of heart damage.

F. T. Shannon.

Therapeutic Effects of ACTH and Cortisone in Rheumatic Fever: Cardiologic Observations in a Controlled Series of 100 Cases. HARRIS, T. N., FRIEDMAN, S. NEEDLEMAN, H. L., and SALTZMAN, H. A. (1956). *Pediatrics*, **17**, 11. 27 refs.

A controlled investigation was undertaken of the efficacy of ACTH and cortisone in the treatment of rheumatic fever in 100 consecutive patients, aged 3 to 17 years, seen at three hospitals in Philadelphia between September, 1950, and June, 1954. The patients were divided into three groups:

Group 1, without carditis, 21 patients;
Group 2, an initial episode of carditis, 48 patients;
Group 3, recurrent carditis, 31 patients.

Within each of these three clinical groups the patients were assigned in rotation to one of three treatment groups—ACTH, cortisone, and control (symptomatic treatment only). ACTH was given intramuscularly in a dosage of 40 mg. daily to children aged 3 to 4 years increasing with the age up to 120 mg. daily in those over 15 years of age. At first cortisone was administered intramuscularly in a dosage of 120 to 300 mg. daily according to age; later, a slightly larger dosage was given by mouth. During the first 48 hours all patients in the series received a larger dose than that determined by age. Hormone treatment was continued until all clinical evidence of activity had disappeared [the criteria of "activity" are not stated] and the erythrocyte sedimentation rate (E.S.R.) had remained at or below 15 mm. in one hour for at least a week; the dosage was then gradually reduced until the drugs were finally discontinued, usually after 8 to 10 days. Salicylates were not given to patients in the treated groups, and the dosage of such drugs in the control groups "was kept to a minimum" (less than ½ gr. per lb. (70 mg. per kg.) body weight daily). Injections of penicillin or sulphonamides were given prophylactically in all cases, and the hormone-treated

patients received 1 to 2 g. potassium citrate daily and a low-salt diet.

When the patients were discharged from hospital no significant differences were observed between the hormone-treated and control groups with carditis as regards the disappearance or persistence of murmurs or the appearance of new murmurs, the degree of transmission of apical systolic murmurs, or the duration of episodes of pericardial friction. [Dividing the patients into nine groups meant that there were very few in each group: the maximum was seventeen.] The appearance of new murmurs in the group without carditis initially was very exceptional. Changes in the pattern of the electrocardiogram and in heart size were so widely scattered within each treatment group that quantitative comparisons were not possible.

There were two deaths in the series: one control patient died after 6 weeks' illness, while another child, who was given ACTH for 6 weeks but showed "evidence of continued rheumatic activity", died 4 weeks after completing treatment. [The abstracter wonders whether these deaths could have been prevented by giving the benefit of specific treatment in the control case after it was apparent that there was no improvement, and by prolonging or changing treatment in the ACTH-treated case. In the latter, the criteria for the duration of treatment, as laid down by the authors, do not appear to have been observed.]

There was no difference in the response to hormone treatment, so far as cardiac murmurs were concerned, whether treatment was started within one week or within 2 or more weeks of the onset of the disease. Rebound phenomena occurred in two-thirds of the cases when the drugs were withdrawn and were maximum in the second week; in one-half of these there was a rise in the erythrocyte sedimentation rate only, while in the other half there were clinical signs as well. Serious intercurrent infections in the cortisone group included pyogenic meningitis (one case) in spite of daily prophylactic injections of penicillin. Hypertension developed in thirteen of the hormone-treated patients and oedema, with or without ascites, in 21.

The authors found no evidence that the hormones, as administered, exerted a beneficial effect on the disease, particularly the cardiac manifestations; as they point out, however, the patients were observed only during the period in hospital and it is possible that benefits from such treatment may become apparent at a later stage.

John Lorber.

Antistreptolysin and Streptococcal Antihyaluronidase Titres in Sera of Hormone-Treated and Control Patients with Acute Rheumatic Fever. HARRIS, T. N., NEEDLEMAN, H. L., HARRIS, S., and FRIEDMAN, S. 1956). *Pediatrics*, **17**, 29. 2 figs, 18 refs.

A minimum of four samples of serum were taken from each of the patients with rheumatic fever included in the previous investigation (see previous Abstract), and their antihyaluronidase and antistreptolysin-O titres estimated, two being tested within 4 days of the patient's admission and two after an interval of one month. [For details of the methods employed the original paper should be consulted.] In the majority of patients receiving symptomatic treatment only there was no change in either titre after one month's interval, whereas in the majority of those given cortisone or ACTH there was a fall in both titres. The results are analysed by advanced mathematical methods.

John Lorber.

Prevention of Residual Endocarditis after Rheumatic Fever by Hormone Therapy. (La prévention des endocardites résiduelles de la maladie de Bouillaud par l'hormonothérapie.) JEUNE, M., and FAYOLLE, M. C. (1956). *Pédiatrie*, **11**, 69. 4 refs.

The authors state that although the effect of cortisone, ACTH (corticotrophin), and aspirin in preventing residual carditis following rheumatic fever has recently been shown to be about equal by workers in Britain and the U.S.A., it has been their experience at the Hôpital Debrousse, Lyons, that hormone therapy is definitely superior.

In an uncontrolled series of 83 cases of first attacks of rheumatic fever treated between October, 1951, and May, 1955, there were 31 without and 52 with cardiac involvement. The first eight patients were given only one 15-day course of ACTH, but the remaining 75 were treated according to a fixed regimen, the dose of steroids being governed by the erythrocyte sedimentation rate (E.S.R.), determined twice weekly, the object being to reduce it as quickly as possible. The initial daily dose of ACTH given orally was 2 to 4 mg. per kg. body weight, this being equivalent to 4 mg. hydrocortisone or 1 mg., prednisone. If the fourth E.S.R. reading was still above 20 mm. in one hour the dose of ACTH was increased by 25 mg. daily; if it remained below 20 mm. on two consecutive occasions the dose was reduced by a similar amount. In this way a gradual reduction was effected, the total course usually lasting not more than 6 weeks in the most favourable cases, about 2 months in less favourable, and 4 months or more in the most serious cases. If the E.S.R. rose again after treatment steroid therapy was repeated. Concurrently, benzyl-penicillin was given in weekly doses of 300,000 units together with 500 mg. ascorbic acid and 1 g. potassium chloride daily, bed rest being maintained for 2 weeks after the end of hormone administration.

In all, 71 children (seven out of the first eight treated and 64 out of the remaining 75) were followed up for periods of from 6 to 36 months. Of these, fifteen (six from the former group) showed residual endocarditis.

Of forty patients whose treatment was started within 2 weeks of the onset of symptoms, only four had residual carditis, compared with five of the other 24, whose treatment was delayed. All nine cases of endocarditis were in the group of forty who had cardiac signs when treatment was started. There were no deaths in the series.

Thus the incidence of cardiac sequelae following hormone therapy was only 14 per cent., compared with 70 per cent. in patients treated before hormone therapy was available. In the Anglo-American investigations mentioned above, in which no significant difference was

found between the effects of hormones and aspirin, the dose of ACTH was only one-third of that employed in the present series. The authors thus suggest that although there has lately been a reduction in the severity and incidence of rheumatic fever, partly due no doubt to the use of antibiotics in acute tonsillitis, early admission to hospital and the institution of adequate hormone treatment are the factors most likely to reduce the risk of residual cardiac damage in this condition.

P. I. Reed.

Q-T Interval in Rheumatic Heart Disease. KORNEL, L., and BRAUN, K. (1956). *Brit. Heart J.*, **18**, 8. 1 fig., 19 refs.

A study of the Q-T interval in electrocardiograms (ECGs) from five groups of patients with rheumatic heart disease was made at the Rothschild Hadassah University Hospital, Jerusalem. In all, 164 tracings were examined from 157 subjects, the Q-T interval being corrected for cardiac rate (Q-T*c*) by Taran and Szilagy's modification of Bazett's formula.

Group I, 33 normal subjects in whom the upper limit of Q-T*c* was 0·412 second.

Group II, fifty patients with active rheumatic heart disease, in all but six of whom the Q-T*c* was more than 0·412 sec., ranging from 0·414 to 0·528 sec.

Group III, thirty patients with "subclinical" rheumatic activity, and of these 28 had a prolonged Q-T*c* which varied from 0·415 to 0·468 sec.

Group IV, thirty patients with quiescent rheumatic heart disease, in all but two of whom the Q-T*c* was below the upper limit of normal.

Group V, fourteen patients who had undergone mitral valvotomy, in ten of whom the Q-T*c* was prolonged; in two of these ten cases Aschoff bodies were found on histological examination of the auricular appendage and in two others cellular accumulations resembling Aschoff bodies were seen, whereas in the four cases with a normal Q-T*c* no histological evidence of activity was found.

The incidence of other abnormalities (P-R interval, S-T deviation, T changes) in the ECG in active cases was far below that of prolongation of Q-T*c*. It is therefore concluded that an increased Q-T*c* is a sensitive index of rheumatic activity.

C. Bruce Perry.

Capillary Microscopy in Rheumatic Fever. DAVIS, E., and LANDAU, J. (1956). *A.M.A. Arch. intern. Med.*, **97**, 51. 3 figs, 12 refs.

This paper reports the findings on examination of the capillary patterns in the conjunctiva and nailbed in 100 patients with rheumatic fever or rheumatic heart disease at the Rothschild Hadassah University Hospital, Jerusalem. This group included both active and inactive cases. Similar examinations were carried out on a control group of 158 "nonrheumatic patients" [which nevertheless included thirty cases of rheumatoid arthritis and eleven of collagen diseases].

A characteristic capillary pattern was found in the conjunctiva in 79 and in the nailbed in 31 of the 100 rheumatic patients, the corresponding figures for the control group being eleven and seven. The special feature seen in the conjunctiva was the repeated subdivision of vessels and the abrupt thinning of the end capillaries, which was in marked contrast to the usual picture of an interlacing latticework of conjunctival vessels. In the nailbed several capillaries would often branch out from a common stem. Analysis did not show any correlation of these capillary patterns with sex, age, or the activity or chronicity of the rheumatic process.

A higher incidence of these changes was found among 26 non-rheumatic members of 22 families in which there were 32 cases of rheumatic fever or rheumatic heart disease than among controls. It is therefore thought possible that the patterns may be present before the onset of rheumatism and may be associated with a rheumatic diathesis rather than with the disease itself. The presence of these capillary signs may help in the diagnosis of borderline cases.

G. W. Csonka.

Prevention of Rheumatic Fever by Treatment of Previous Streptococcic Infections. MORRIS, A. J., CHAMOVITZ, R., CATANZARO, F. J. and RAMMELKAMP, C. H. (1956). *J. Amer. med. Ass.*, **160**, 114. 7 refs.

Although it has been shown that adequate treatment of streptococcal infections with penicillin will prevent the subsequent development of rheumatic fever, it has never been clearly determined whether sulphonamides, which are still widely used for the treatment of streptococcal pharyngitis, have a similar protective effect. At a U.S. Air Force base a total of 291 patients with pharyngitis were treated with 2 g. sulphadiazine followed by 1 g. every 6 hours for 5 days. Group-A haemolytic streptococci were isolated from the oropharynx of 261 patients, who were then compared with 264 similar patients who received no specific treatment.

After 9 days 66 per cent. of the treated group and 88 per cent. of the control group still harboured the organism; the figures at the end of 13 days were 82 per cent. and 85 per cent. respectively. A relapse occurred in 21 (8 per cent.) of the treated patients compared with seven (2·7 per cent.) of the controls. Suppurative complications (peritonsillar cellulitis, otitis media, or sinusitis) developed in eleven (4·2 per cent.) of the patients receiving sulphadiazine and in seventeen (6·5 per cent.) of the control group. The reduction in the incidence of these complications in the treated group was confined to the first week, the incidence during the second week being the same in both groups.

Of the treated patients, fourteen (5·4 per cent.) subsequently developed rheumatic fever and a further six mild symptoms suggestive of rheumatic fever. Rheumatic fever occurred in eleven (4·2 per cent.) of the control subjects.

It is concluded that sulphadiazine in the dosage used does not eradicate the infecting organism or prevent the development of rheumatic fever, although it reduces the incidence of suppurative complications while it is being given. The higher relapse rate after the treatment of streptococcal pharyngitis with sulphadiazine is presumably due to inhibition of the organism delaying the development of immunity to it.

[These findings do not of course in any way invalidate

the use of sulphonamides in the prophylaxis of haemolytic streptococcal pharyngitis and of rheumatic relapses.]

C. Bruce Perry.

Observations on the Electrocardiographic Changes in Acute Rheumatism. FIFE, R., and MURDOCH, W. R. (1955). *Glasg. med. J.*, **36**, 379. 1 fig., 37 refs.

A review is presented of the electrocardiographic changes found in 62 cases of acute rheumatic carditis in patients aged 4 to 40 years who were admitted to Law Hospital, Carlisle, within 6 weeks of the onset of the attack.

Auricular fibrillation was present in three cases. The P-R interval was prolonged in seven (11 per cent.). Deviation of the S-T interval occurred in sixteen cases, but six of the eight patients in whom it was elevated had pericarditis, while in three of those in whom it was depressed ventricular hypertrophy was also present.

The presence of negative T-waves in Leads V1 to V4 is normal in children, but in ten cases of the present series it was accepted as evidence of carditis as subsequent records showed a lessening of the negativity. In four cases the changes were slight.

The existence of several different standards of normality for the Q-T interval makes the significance of small increases difficult to assess; according to one standard the interval was prolonged in 27 of the cases, but according to another standard only in three.

The authors are of the opinion that changes in the S-T segment and the T-wave are of more value in the diagnosis of carditis in acute rheumatism than an increase in the Q-T interval and they stress the importance of serial tracings. They suggest that no definite conclusion as to the prognostic value of electrocardiographic findings in rheumatic carditis is justified in the present state of knowledge.

[It is evident that while electrocardiographic changes occur in a proportion of patients with rheumatic carditis the diagnosis must usually be made on other grounds.]

C. W. C. Bain.

Estimation of Adrenocortical Hormones in Patients with Rheumatic Carditis undergoing Treatment. (Исследование гормонов коры надпочечников у больных с кардиальной формой ревматизма в связи с гормональной терапией) TOLOKNOVA, E. A. (1955). *Ter. Arkh.*, **27**, 68, No. 8. 5 figs.

Serial estimations of adrenocortical hormones were made on a group of 42 patients with rheumatic carditis, of whom 25 were treated with ACTH, eleven with "butadion", and six with salicylates. The serum 11-oxysteroid level was estimated by the method of Cornelius and MacDonald (as modified by Bush), while urinary 17-ketosteroid excretion was determined by Zimmerman's method as modified by Preobrazhenskii.

The findings may be summarized as follows:

(1) The urinary content of 17-ketosteroids is lowered in most cases of rheumatic carditis.

(2) The serum 11-oxysteroid level may be lowered, normal, or even raised during certain forms of treatment.

(3) ACTH causes a sharp rise in the serum level of these hormones, but this tends to fall after the cessation of treatment.

(4) Butadion causes similar but less marked changes.

(5) Salicylates cause a slight rise in the urinary excretion of 17-ketosteroids.

In many of the cases in all three groups the blood 11-oxysteroid level and the urinary excretion of 17-ketosteroids before treatment were lower than the average for the control subjects. *L. Firman-Edwards.*

Incidence of Asymptomatic, Active Rheumatic Cardiac Lesions in Patients submitted to Mitral Commissurotomy and the Effect of Cortisone on these Lesions. Clinical and Histopathological Study of Sixty Cases. GIL, J. R., RODRIGUEZ, H., and IBARRA, J. J. (1955). *Amer. Heart J.*, **50**, 912. 7 figs, 16 refs.

The incidence of lesions of active rheumatic fever in the auricular appendage at the time of mitral commissurotomy was studied in sixty patients at the National Institute of Cardiology, Mexico City. Cortisone was given to fourteen of the patients before and after operation. Histologically, the cases were divided into three groups:

(1) Those in which there were Aschoff nodes, cellular infiltration, and fibrinoid necrosis;

(2) Cases similar to (1) but without fibrinoid necrosis;

(3) Cases in which Aschoff nodes were observed, but there was no fibrinoid necrosis or acute cellular infiltration.

Two healing stages with fibrosis were recognized. On the basis of these criteria, 36 of the sixty patients showed rheumatic activity, nine showed signs of healing, and fifteen had healed lesions. Active rheumatic lesions were infrequent and less severe in the cortisone-treated patients than in the controls. Relapse occurred after operation in some of the cases in both the treated and untreated groups, but the authors nevertheless consider that the effect of cortisone on the prevention of these relapses merits further study.

[The statement that "it is certain that cortisone has a beneficial effect on rheumatic active lesions" is not warranted by the results of this investigation.]

G. Loewi.

Studies of Bacterial Throat Flora during Chemoprophylaxis of Rheumatic Fever. MILLER, J. M., and MASSELL, B. F. (1956). *New Engl. J. Med.*, **254**, 149. 1 fig., 35 refs.

The bacteriology of the throat of 199 patients with a history of acute rheumatic fever who were receiving prolonged treatment with sulphadiazine or penicillin was compared with that of 94 patients with a similar history who were not receiving chemoprophylaxis. The investigation, which was carried out at the House of the Good Samaritan, Boston, extended over 12 months, throat swabs being taken at intervals throughout this period. Of the treated patients, 59 received penicillin and sixty sulphadiazine.

The medium used, sheep-blood-agar, does not support the growth of *Haemophilus influenzae*; therefore no

information concerning the presence or absence of this organism is available. The incidence of *Streptococcus viridans* and of *Staphylococcus albus*, the most commonly found organisms, was the same in both of the treated groups and the control group. The incidence of *Staph. aureus* was higher in the two treated groups than in the controls, whereas pneumococci were more frequently present in the control group than in either of the treated groups. None of the throat swabs from the patients receiving penicillin or sulphadiazine yielded Group-A beta-haemolytic streptococci. Coliform bacilli were isolated from throat swabs from 10 per cent. of the penicillin-treated patients, but in none of these was there clinical superinfection of the respiratory tract by the organisms. No information was available concerning fungus infections, but there were no clinical manifestations of moniliasis in the series. *E. G. Rees.*

Studies of C-reactive Protein in Patients with Rheumatic Heart Disease. I. Lack of Correlation between C-reactive Protein and Aschoff Bodies in Left Auricular Appendage Biopsies. ELSTER, S. K., and WOOD, H. F. (1955). *Amer. Heart J.*, **50,** 706. 2 figs, 19 refs.

The significance of Aschoff bodies found in the auricular appendage at mitral commissurotomy is as yet unknown. In the present study, reported from the Rockefeller Institute for Medical Research, New York, the histopathological findings in the auricular appendages obtained at operation from twenty patients were correlated with the presence or absence of C-reactive protein. This abnormal protein is found in a variety of disorders, including rheumatic fever, and although non-specific is a very sensitive indicator of activity in rheumatic fever. Aschoff bodies were found in seven of the biopsy specimens, but the patients from whom these were obtained did not differ significantly from the other patients in regard to clinical course, erythrocyte sedimentation rate, leucocyte count, and electrocardiographic findings. While the serum of only two of these seven patients contained C-reactive protein this type of protein was present in the serum of four of the thirteen patients without Aschoff bodies.

In discussion the authors state that the apparent lack of correlation between the presence of C-reactive protein and that of Aschoff bodies may indicate that the pathological process is not sufficiently active to lead to the production of this abnormal protein, and suggest that in such cases the degree of rheumatic activity may have little clinical significance. *G. W. Csonka.*

Therapy of Rheumatic Fever. Comparison of Results obtained with Salicylates, Cortisone or Corticotrophin, Phenylbutazone, and Combination of Sodium Salicylate, *para*-Aminobenzoic Acid, and Cortisone. [In English.] KALLIOMAKI, L. (1955). *Acta med. scand.*, **152,** 473. 1 fig., 15 refs.

In a previous report (*Nord. Med.*, 1954, **61,** 296) the author compared the results of treatment of rheumatic fever with salicylates and with cortisone or corticotrophin. The present report from the Medical Clinic of the University of Turku, Finland, concerns 24 further patients, ten of whom were treated with 300 to 600 mg. phenylbutazone daily for 6 to 53 days, while the remaining fourteen received a combination of sodium salicylate (2·8 to 4·2 g.), *para*-aminobenzoic acid (1·6 to 2·4 g.), and cortisone (25 to 300 mg. daily), the first two being given together for an average of 44 days and the last for an average of 19 days. The results in these two groups are compared with each other and with those previously reported.

In the first 2 weeks the erythrocyte sedimentation rate (E.S.R.) fell more quickly in the group receiving combined therapy, but when the cortisone was stopped in the third week there was a rebound; after the third week the E.S.R. fell in a similar manner in all four groups. However, apart from this there was no definite difference between the four groups except that possibly the group receiving cortisone or corticotrophin alone did less well than the others. It was not possible to assess the different forms of treatment on the duration of the carditis. It is concluded that the treatments described are of equal value. *C. Bruce Perry.*

Post-operative Reactivation of Rheumatic Fever. (Reactivation postopératoire de la maladie rhumatismale.) VAN BOGAERT, A., and FANNES, E. (1956). *Acta cardiol.* (*Brux.*), **11,** 141. 2 figs, 8 refs.

Rheumatic Fever and its Treatment. (La maladie de Bouillaud et son traitement.) CHAPTAL, J., JEAN, R., and CAMPO, C. (1956). *Sem. Hôp. Paris.*, **32,** 1175. 2 figs.

Instability of Auriculoventricular Conduction in Acute Rheumatic Fever. I. Frequency and Extent. II. Effect of Position on First Degree Heart Block. SUTTON, G. C., SCHAFFNER, F., SCHERBEL, A. L., and CRANE, T. (1956). *U.S. armed Forces med. J.*, **7,** 481 and 489. 24 refs.

Mental Forms of Sydenham's Chorea. (Formes mentales de la chorée aiguë de Sydenham.) FAU, R., and CHATEAU, R. (1956). *J. Méd. Lyon*, **37,** 279.

Problem of Subclinical Rheumatic Carditis. TEDESCHI, C. G., and WAGNER, B. M. (1956). *Amer. J. med. Sci.*, **231,** 382. 17 refs.

Tonsillectomy in Children with Rheumatism. (Amigdalectomia en niños afectados de reumatismo infantil.) FRASCHINA, H. L., and FERNÁNDEZ MENDY, J. (1956). *Rev. argent. Reum.*, **21,** 2.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Bone Marrow in Rheumatoid Arthritis. (La moelle osseuse dans la polyarthrite chronique évolutive.) THIERS, H., VIGNON, G., MOREL, L., and PATET, J. (1955). *Rev. Rhum.*, **22,** 709. 6 figs, 35 refs.

The authors have studied the cytology of the bone marrow in sixteen adult patients suffering from rheuma-

toid arthritis [no further clinical details are given]. In most cases cells of the lymphocytic series, large mononuclear leucocytes, histiocytes, and plasma cells showed some increase in numbers beyond normal limits, the last-named in particular being almost invariably increased, sometimes to a degree constituting more than 5 per cent. of the total. They showed all the characteristic cytological features, but were sometimes multinucleate.

The other constant abnormality was the presence of iron-deficiency changes in the erythroid series. These became obvious at the polychromatic stage, the cytoplasm appearing thin and its colour changing from pink to greenish-grey at the periphery, while the nucleus appeared to be prematurely senile. Cells in the orthochromatic stage showed a very small pyknotic nucleus and smudgy cytoplasm. Cells of the eosinophil and neutrophil series were only a little reduced in number; some macropolycytes and toxic granulation were seen.

Hormonal treatment resulted in a return towards normal of all the features described, except those indicating iron deficiency. The authors speculate on the connexion between plasmocytosis of the marrow, the increased serum globulin content, and amyloidosis in rheumatoid arthritis. *S. C. Milazzo.*

Prednisone in the Treatment of Rheumatoid Arthritis. COHEN, A., TURNER, R., and DUNSMORE, R. (1955). *New Engl. J. Med.*, **253**, 1150. 10 refs.

33 patients with severe rheumatoid arthritis were treated with prednisone, a new steroid with adrenocortical activity. The daily dosages ranged from 30 to 60 mg. initially to a daily maintenance dosage of 12·5 to 20 mg. A potency ratio of 3:1 or 4:1 as compared with cortisone was established. Objective improvement with a decrease in joint pain, tenderness and swelling and an increase in range of motion of affected joints occurred rapidly after the initiation of prednisone therapy. A significant decrease occurred in eosinophil counts and a moderate decrease in elevated erythrocyte sedimentation rates. Hypertension was augmented in one patient with essential hypertension, but hypertension in another caused by cortisone was relieved during prednisone administration. Prednisone had no adverse effects on blood sugar, serum sodium and potassium, or blood urea nitrogen levels. No patient had evidence of oedema, and no glycosuria developed. One patient had a slight loss in body weight. one had a definite euphoria, and four had slight rounding of the face. A chronically scarred duodenal cap in one patient was adversely affected during 5 months' administration of prednisone by virtue of a pylorospasm.—[*Authors' summary.*]

Prednisone and Prednisolone Therapy in Rheumatoid Arthritis. Clinical Evaluation based on Continuous Observations for Periods of Six to Nine Months. BOLAND, E. W. (1956). *J. Amer. med. Ass.*, **160**, 613. 6 figs, 11 refs.

The recently introduced synthetic steroids prednisone and prednisolone were administered to 141 patients suffering from severe active rheumatoid arthritis. The series included a group of 32 patients not previously treated and these were given the steroids as initial treatment in oral doses of 10 to 20 mg. daily. For all patients the dosage was gradually reduced to maintenance levels by decrements of 1·25 to 2·5 mg. at intervals of 5 to 14 days. In most cases subjective relief was recorded within 24 hours, and objective improvement could be measured after 2 to 4 days. During a period of observation ranging from 6 to 9 months satisfactory improvement was maintained in more than 50 per cent. of the patients. It was considered that larger doses of hydrocortisone would have been necessary in order to produce similar results, and this impression was confirmed by the results in patients given prednisone and prednisolone who had previously been treated with hydrocortisone.

However, most of the patients experienced untoward reactions, notably ecchymotic skin lesions, vasomotor symptoms, and digestive complaints; on the other hand there were few cases of oedema and in no case was there evidence of hypertension or potassium loss.

As shown by biological experiments prednisone and prednisolone exhibit an adrenocortical hormonal activity which is three to four times greater than that of their analogues, cortisone and hydrocortisone. It would appear, therefore, that in the treatment of rheumatoid arthritis prednisone and prednisolone are to be preferred to hydrocortisone, except for patients with peptic ulcer and those in whom gastric irritation results from the administration of the new steroids, which provoke the secretion of about twice as much free hydrochloric acid as does hydrocortisone. *A. Garland.*

Pleural Effusion complicating Rheumatoid Arthritis. EMERSON, P. A. (1956). *Brit. med. J.*, **1**, 428. 28 refs.

In this paper from the Brompton Hospital, London, the author describes the cases of six patients who suffered from polyarthritis of the rheumatoid type and who, in exacerbations of their disease, developed pleurisy with effusion. The patients were thoroughly investigated to exclude other causes of pleurisy, and during a period of observation ranging from 2 to 4½ years none of them has shown any clinical, radiological, or laboratory evidence to suggest any cause for the effusions other than the rheumatoid process. The effusions were found to be very persistent; in two cases they were still present after 2 years.

In the author's view these pleural effusions were due to involvement of the pleura in the rheumatoid process. *J. Warwick Butler.*

Rehabilitation of the Rheumatoid Arthritic Cripple. LOWMAN, E. W. (1955). *J. S. C. med. Ass.*, **51**, 421.

A combination of medical treatment, rehabilitation, and vocational guidance was given to two groups of patients with active rheumatoid arthritis at the Goldwater Memorial Hospital, New York.

Group I contained 24 severely disabled patients while Group II contained 26 who were less badly disabled but were unable to continue their occupation; later, six patients had to be dropped from each group. Steroid therapy was necessary to control the arthritic process in 25 of the 38 patients and phenylbutazone in eight; only five could be maintained on salicylates alone.

In Group I medical treatment reduced the average "functional deficiency" from −60 per cent. to −53 per cent.; after intensive rehabilitation functional deficiency was −29 per cent., the average duration of treatment being 339 days. One patient was placed in suitable occupation and thirteen were discharged wholly or partly self-sufficient; four patients had to remain in hospital.

In Group II medical treatment reduced the average functional deficiency from −30 per cent. to −13 per cent.; after rehabilitation the figure was −4 per cent., the average duration of treatment being 223 days. All the patients in this group were discharged wholly or partly self-sufficient, seven being placed in suitable work.

The author has found that among the more important factors which help in the selection of patients suitable for rehabilitation are adequate medicinal control of the arthritic process, reasonable mechanical integrity of the joints, and a good psychological outlook on the part of the patient. Other factors which influence selection are the applicability or otherwise of self-help devices and the socio-economic resources of the patient.

B. E. W. Mace.

Involvement of the Kidneys in Rheumatoid Arthritis. (К вопросу о поражении почек при так называемом неспецифическом инфекционном (ревматоидном) артрите) SURA, V. V., and MAKARENKO, I. I. (1955). *Sovetsk. Med.*, **46**.

Analysis of the urine in a group of patients with rheumatoid arthritis at the Lenin Institute of Hygiene, Moscow, showed that 26 had some degree of renal involvement. In sixteen of these cases no other condition was found to account for the urinary changes and the renal lesion was consequently attributed to the rheumatoid arthritis. In three of the cases there was severe albuminuria, some casts, leucocytes, and a few erythrocytes in the urine; in the remainder, however, the albuminuria was slight, and casts and blood cells were scanty. In all sixteen cases treatment with ACTH and cortisone completely cleared up or greatly improved the rheumatic manifestations but had no influence on the urinary findings, nor therefore, the authors conclude, on the renal lesion.

A. Swan.

Zone Electrophoresis in Studies of Serum Proteins, Protein-Bound Polysaccharides and Serum Lipids in Rheumatoid Disease. KUHNS, W. J., and CRITTENDEN, J. (1955). *J. Lab. clin. Med.*, **46**, 398. 3 figs, 24 refs.

At the University of Pittsburgh School of Medicine samples of serum from 32 patients with rheumatoid arthritis or rheumatoid spondylitis, one with rheumatic fever, and two with lupus erythematosus were fractionated on filter paper by the method of Kunkel and Tiselius, using a barbitone buffer at pH 8·6. Staining was carried out for protein with bromphenol blue and mercuric chloride in alcohol, for polysaccharide with basic fuchsin and periodic acid, and for lipids with Sudan black. (The patterns from a number of these runs are illustrated.)

The protein-bound polysaccharide was found to be increased, compared with normal values, particularly in the α_2 fraction. In one case there was a decrease in the serum albumin content. Increases in gamma and alpha globulins were seen in most of the rheumatoid arthritic patients, while the two patients with lupus erythematosus showed increases mainly in the γ-globulin fraction. No consistent abnormality was observed in the lipid pattern.

E. G. L. Bywaters.

Keratitis and Scleritis associated with Felty's Syndrome. OSTRIKER, P. J., OSTRIKER, M., and LASKY, M. A. (1955). *A.M.A. Arch. Ophthal.*, **54**, 858. 1 fig., 14 refs.

Felty's syndrome consists essentially of three elements; chronic rheumatoid arthritis, splenomegaly, and leucopenia. In this case there was also an ocular element with a scleromalacia perforans of the left eye, leading to a severe corneal ulcer and iridocyclitis. The corneal ulcer perforated with loss of the eye, but it may be significant that the perforation followed local cortisone and systemic ACTH therapy. Subsequently the right eye developed a keratitis but this improved following splenectomy.

K. C. Wybar.

Hypophyseal Abnormalities in Rheumatoid Arthritis. PEARSE, A. G. E. (1956). *Rheumatism*, **12**, 29. 6 figs.

Felty's Syndrome. CUDKOWICZ, L. (1956). *Rheumatism*, **12**, 37. 22 refs.

Case of Felty's Syndrome treated with Hydrocortisone and Prednisone. (Osservazioni su un caso di sindrome di Felty trattato con idrocortisone e prednisone.) MORGANO, G., and DE CARLO, M. (1955). *Arch. "Maragliano" Patol. Clin.*, **2**, 901. Bibl.

Clinical and Metabolic Effects of Prednisone and Prednisolone in Rheumatoid Arthritis. NEUSTADT, D. H., MCCLENDON, R., OLASH, F. A., and BEST, M. (1956). *J. Kentucky med. Ass.*, **54**, 131. 2 figs, 10 refs.

Hydrocortisone *versus* Prednisolone in Rheumatoid Arthritis. FISHER, M. (1956). *Lancet*, **2**, 18. 4 refs.

Treatment of Rheumatoid Arthritis with Cortisone and ACTH. (Behandeling van reumatoïde arthritis met cortison en ACTH.) GOSLINGS, J., and CATS, A. (1956). *Ned. T. Geneesk.*, **100**, 903. 7 refs.

Management of Rheumatoid Arthritis—with Particular Reference to Steroid Therapy. COPEMAN, W. S. C. (1956). *N.Z. med. J.*, **55**, 3. 13 refs.

Effect of Intravenous Calcium Gluconate Infusion on the Calcium and Phosphorus Excretion of Patients with Rheumatoid Arthritis. [In English.] HOLOPAINEN, T., and KOSKINEN, H. M. (1956). *Acta rheum. scand.*, **1**, 250. 1 fig., 22 refs.

Ten Cases of Rheumatoid Arthritis treated with PAS and Other Measures over a Two-year Period. HAYNES, B. (1956). *Med. J. Aust.*, **1**, 692. 7 refs.

Scar Development following Hyperpigmentation in Rheumatoid Arthritis. A Proposal for Clinical Investigation. [In English.] FORBECH, V. (1956). *Acta rheum. scand.*, **1**, 241.

(Osteo-Arthritis)

Intra-Articular and Paravertebral Injection of Cortisone in Osteo-Arthritis of Spine. COHEN, A., SCOTT, G. E., TURNER, R. F., and ROSE, I. (1955). *J. Amer. med. Ass.*, **159**, 1724. 2 figs, 15 refs.

At Philadelphia General Hospital cortisone acetate or hydrocortisone acetate was injected into the sacro-iliac joints or into tissue in the region of the cervical, thoracic, and lumbar vertebrae of 46 patients with osteo-arthritis of the spine, on the assumption that the pathological process extends more widely than is shown by radiographic appearances. Up to 23 doses, each of 12·5 to 25 mg., were given, usually at intervals of one or 2 weeks. The technique of injection is described and illustrated with diagrams.

Of the 46 patients, 37 received cortisone and nine hydrocortisone; neither drug appeared to have any advantages over the other. The results were judged by subjective relief of pain.

Of the 26 patients with cervical osteoarthritis, fourteen claimed to receive marked or moderate relief, while of fourteen treated by sacro-iliac injection, eleven experienced such relief. (Similar figures were obtained later with a trial of prednisolone acetate in 22 comparable cases.) Generally, if no benefit was seen after four injections further attempts were of little avail.

[The author's views on the role of heavy domestic work and other occupational factors in the aetiology of osteo-arthritis require to be substantiated.]

J. N. Agate.

Osteo-Arthritis of the Cervical Spine. Stage and Treatment. KUHNS, J. G. (1956). *New Engl. J. Med.*, **254**, 60. 4 figs, 14 refs.

Osteo-arthritis of the cervical spine is a progressive disorder—in most cases slowly progressive—in which, clinically, there are three stages.

In the early stage, in which the radiological changes are slight, the symptoms are pain and stiffness and spasm in the antigravity muscles of the neck; in the second stage, in which the radiograph shows narrowing of the intervertebral disks, the chief symptom is pain referred to the dermatomes of the nerve roots that are irritated; in the third stage there are advanced radiological changes with severe limitation of movement, deformity in the cervical region, and local and root pain.

Symptoms in the early stage are most effectively treated by temporary application of a padded collar; this should be worn until symptoms subside but should be removed several times a day for local heat treatment. Endocrine disturbances should be corrected and foci of infection removed. The aim of treatment in the second stage is directed to relief of pressure on the nerves, for which a firm bed without pillows or at most a small pillow under the nape of the neck is advised. Heat treatment is also given. In most cases relief follows the almost continuous application of traction of 5 to 10 lb. (2·2 to 4·5 kg.) to the cervical spine with the patient supine on a firm bed.

If no improvement in root pain follows traction for 2 weeks the pressure on the nerve must be relieved surgically. In the third stage traction may give temporary relief, but the most effective treatment is application of a firm collar, fitting well over the shoulders and supporting the occiput and chin; this can be made of plastic material from a plaster model. In these cases medical supervision must continue for the remainder of the patient's life.

Kenneth Stone.

Osteo-Arthritis. An Approach to Surgical Treatment. TRUETA, J. (1956). *Lancet*, **1**, 585. 13 figs, 14 refs.

Obesity and Degenerative Joint Disease. SILBERBERG, M., JARRETT, S. F., and SILBERBERG, R. (1956). *A.M.A. Arch. Path.*, **61**, 280. 6 figs, 15 refs.

(Spondylitis)

Ankylosing Spondylitis. MIDDLEMISS, J. H. (1956). *J. Fac. Radiol.* (*Lond.*), **7**, 155. 28 figs.

Ankylosing spondylitis is a self-limiting disease, affecting predominantly young males; it may be arrested at any point, or may run its full course, ending with ossification of the tissues involved, that is primarily connective tissue. The sites mainly involved are the sacro-iliac joints and the joints and ligaments of the spine; other sites, however, are not uncommonly affected especially around the pelvic girdle, for example, the symphysis pubis, the outer borders of the iliac bones, and the ischial tuberosities.

The radiological changes are those of bone destruction followed by repair; thus, there is osteoporosis of the cortex, followed by bone reaction, calcification, and re-ossification; the last named extends beyond the original bone margin but still remains in the connective tissue planes. The disease is progressive, usually starting in the sacro-iliac joints, the spine being then involved in an ascending direction, though some areas of the spine may be spared. Involvement of the connective tissue attachments, especially those of the greater trochanter, the os calcis, and also of the joints of the extremities may occur, usually as a late manifestation. The detailed bone changes in the peripheral joints are indistinguishable from those seen in rheumatoid arthritis, but the over-all pattern is different (the main differences are set out in parallel columns in the original paper.)

The author points out that the general radiological pattern of ankylosing spondylitis in women differs from that in men; in the latter the so-called "bamboo spine" is the typical appearance, whereas women tend to show the "streaky" type of spine. The common features of the disease in females are thus:

(1) marked involvement of the posterior spinal articulations;

(2) little or no ligamentous ossification;

(3) osteoporosis;

(4) often considerable calcification of the costal cartilages.

It is stressed that the radiological appearances of ankylosing spondylitis can be explained in terms of inflammation, reaction, and repair. *L. G. Blair.*

Spondylitis of Juvenile Rheumatoid Arthritis. BARKIN, R. E., STILLMAN, J. S., and POTTER, T. A. (1955). *New Engl. J. Med.*, **253**, 1107. 8 figs.

Spinal involvement in juvenile rheumatoid arthritis has occasionally been noted in the literature, but has never been adequately investigated. The present authors have therefore undertaken a survey of all the cases of Still's disease seen over the last 40 years at the Robert Breck Brigham Hospital, Boston (which is largely devoted to rheumatic diseases), in order to determine the incidence and nature of the spondylitis. Clinical or *x*-ray evidence of spinal involvement was found in 57 (80 per cent.) of 71 cases, the areas most commonly affected being the neck and lower back. Calcification of the paravertebral ligaments was, however, unusual, being noted in only two cases in this series. The symptoms of spinal involvement generally appeared at, or soon after, the onset of the illness, and one of the ultimate results was a shortening of stature owing to interference with the normal growth of the spine. In no case was spinal arthritis present in the absence of peripheral joint involvement.

In the entire series there were 45 female children and 26 male, in general a similar distribution to that commonly seen in rheumatoid arthritis in adults. Of the 57 patients with evidence of spinal involvement, 37 were female and twenty male—a distribution differing significantly from that of spondylitis in adults and suggesting that the disease is part of the process of juvenile rheumatoid arthritis and not a true spondylitis *sui generis* as in most adults. *W. S. C. Copeman.*

Serum Proteins, Glucoproteins, and Lipids in the Various Clinical Forms of Ankylosing Spondylitis. (Protides, glucides et lipides sériques dans les diverses formes cliniques de la spondylarthrite ankylosante.) JACQUELINE, F., and GROULADE, J. (1955). *Rev. Rhum.*, **22**, 735. 3 figs, 25 refs.

At the Centre for Research in the Rheumatic Diseases, Aix-les-Bains, the authors have studied the serum protein content and pattern in 54 cases of ankylosing spondylitis and in 32 normal male control subjects, other cases of ankylosing spondylitis with associated diseases likely to produce changes in the serum proteins being excluded. Zone electrophoresis on paper was followed by staining with naphthalene black for protein, periodic-acid-Schiff stain for glycoprotein, and Sudan black for lipid. In addition, an estimate of the total serum glyco- and lipoprotein content was made by staining the serum on paper without electrophoresis and comparing it with a standard pooled serum from a group of healthy blood donors aged between 30 and 40. The cases were divided into two groups—those with, and those without, peripheral joint involvement. The patients showing only spinal disease were further divided into:

(1) those in whom the process was relatively painless, the course slow, and radiography showed intervertebral bony bridges and no osteoporosis;

(2) those with more painful and disabling disease, with early apophyseal joint fusion, much vertebral rarefaction, and little bridging.

Purely spinal cases without osteoporosis showed a slightly, in some cases a considerably, increased serum albumin content, in contrast to the hypoalbuminuria in the other cases. The level of the α_2 globulins, and especially that of the associated glycoproteins, was elevated, the glycoprotein level corresponding with the activity of the disease process. The authors consider that in this group the serum glycoprotein content gives a better indication of activity than does the erythrocyte sedimentation rate or the severity of symptoms. Cases with spinal osteoporosis invariably showed a considerable lowering of the serum albumin content, and a persistent elevation of that of α_2 globulin and glycoprotein. The patients with peripheral joint involvement had a lowered serum albumin and a raised α_2-globulin content and a greater increase in γ globulin than in the preceding groups. The increase in the total and α_2 glycoprotein level and the erythrocyte sedimentation rate paralleled the degree of clinical activity of the disease. The serum lipid content showed little change throughout, apart from that which would be expected to result from age.

S. C. Milazzo.

Ankylosing Spondylitis with Aortitis and Aortic Insufficiency. (Spondilite anchilosante con aortite e insufficienza aortica.) LUCHERINI, T., and CECCHI, E. (1956). *Minerva med. (Torino)*, **47** (1), 43. 9 figs, 33 refs.

A case of ankylosing spondylitis with aortitis and aortic insufficiency in a man aged 38 is reported. The clinical appearance excludes rheumatic or syphilitic aetiology of the cardiac and aortic lesion. The possible rheumatoid nature of the affection is suggested by an analogy with the cases reported by Bauer, Clark, and Kulka (1951). The significance of the syndrome is discussed in the light of modern concepts of rheumatic heart disease.—[*Authors' Summary.*]

Reference.

Bauer, W., Clark, W. S., and Kulka, T. P. (1951) "Proc. Amer. rheum. Ass., 1951." *Annals of the Rheumatic Diseases*, **10**, 470.

Iritis in Ankylosing Spondylitis. WEEREKOON, L. M., and GOLDING, C. (1955). *Ceylon med. J.*, **3**, 80. 2 tables, 6 refs.

26 cases seen at the Western Ophthalmic Hospital, London, were divided into two groups—fifteen with established spondylitis, and eleven with iritis as the presenting symptom and positive *x* rays of the sacro-iliac joints. In all cases the exudate in the anterior chamber was thick and gelatinous-looking or took on the appearance of a cob-web coagulum and was sufficiently typical to warrant *x*-ray examination of the sacro-iliac joints whenever it was seen. Cortisone did not usually seem to be of much benefit. *E. J. Somerset.*

Spondylarthritis and the Fiessinger-Leroy-Reiter Syndrome. Two Aspects of the Same Rheumatoid Disease. (Spondylarthrite ankylosante et syndrome de Fiessinger-Leroy-Reiter. Deux aspects de la même maladie rhumatismale.) MARCHE, J. (1955). *France méd.*, **18**, 5.

Ankylosing Spondylarthritis and the Fiessinger-Leroy-Reiter Syndrome. (Spondylarthrite ankylosante et syndrome de N. Fiessinger-Leroy-Reiter.) MARCHE, J. (1955). *France méd.*, **18,** 43.

Heart in Ankylosing Spondylitis. (La coeur dans la spondylarthrite ankylosante.) RUFFLE, R., and FOURNIE, A. (1956). *Rhumatologie*, **1,** 1. 17 refs.

(Miscellaneous)

Specific Therapy for Salicylism. SCHREINER, G. E., BERMAN, L. B., GRIFFIN, J., and FEYS, J. (1955). *New Engl. J. Med.*, **253,** 213. 4 figs, 24 refs.

The authors state that of all fatal cases of poisoning in the U.S.A. due to solids and liquids 4 per cent. are attributed to salicylates, usually aspirin. They describe two cases of salicylate poisoning seen at Georgetown University Hospital, Washington, D.C., one of which—believed to be the first—was successfully treated by haemodialysis by means of the Kolff artificial kidney.

The first patient, a 44-year-old man, was admitted in a comatose condition when the blood salicylate level was found to be 90 mg. per 100 ml. Dialysis was begun 7½ hours later and within 2 to 3 hours the patient was conscious and able to speak rationally. The dialysis was continued for 6 hours during which time 9·4 g. salicylate was recovered, the blood salicylate concentration falling from 90 to 30 mg. per 100 ml. No salicylate was detected in the blood by the third day, and the patient made an uneventful recovery. Although seven empty aspirin bottles were found at the man's home, representing a total of 210 g. of the drug, the patient denied attempted suicide, but stated that about 8 weeks before admission he had begun to take aspirin for headaches, increasing the amount until he was taking fifty tablets a day.

The second case was that of a young woman aged 19 who was drowsy but conscious on admission. Speech was slurred and she complained of a "roaring sound" in the ears. As some 30 hours had elapsed since she had taken the aspirin (stated to be about 40 g.) conservative treatment was given in the form of intravenous administration of fluids and sodium lactate. About 8·4 g. salicylate was excreted in the urine, and the serum salicylate concentration declined from 91 mg. per 100 ml. on admission to 25 mg. per 100 ml. within 1½ days, and by the third day no salicylate was detected in the serum. After severe mental disturbances, manifested by visual hallucinations and maniacal behaviour, the patient reverted to normal behaviour on the fifth day, and was discharged one day later to the care of her family and a psychiatrist.

In an addendum to the paper reference is made to another case in which 166 g. aspirin was taken, the patient being admitted to hospital 16 hours later with a blood salicylate concentration of 115 mg. per 100 ml. This was reduced to 29 mg. per 100 ml. after dialysis for 7 hours; this patient recovered consciousness but eventually died 5 days later.

The authors conclude by pointing out that on the evidence at present available the selection of patients for treatment by dialysis must be tentative, but that patients exhibiting signs of involvement of the central nervous system will probably benefit from the procedure. In view of the danger of damage to the brain they emphasize the importance of rapid removal of salicylate from the body, and urge that salicylism should be regarded as an acute medical emergency. *R. Wien.*

Effectiveness of Salicylamide as an Analgesic and Anti-rheumatic Agent. Evaluation of the Double Blindfold Technique for studying Analgesic Drugs. BATTERMAN, R. C., and GROSSMAN, A. J. (1955). *J. Amer. med. Ass.*, **159,** 1619. 17 refs.

From Flower and Fifth Avenue Hospitals (New York Medical College), New York, the authors report the results of a clinical comparison of aspirin, a placebo, and salicylamide in the treatment of 73 out-patients with painful arthritic conditions. The double-blindfold technique was used, the dose of each drug was 0·6 g. every 4 hours, and assessment of the results was based on subjective reports. All results were subjected to statistical analysis.

The over-all efficacy (the criteria of which are defined) appeared to be about 60 per cent. for each drug. Mild untoward reactions were noted in 25 per cent. of those given aspirin, in 17 per cent. of those given the placebo, and in 31 per cent. of those receiving salicylamide. Asked to state a preference for one medicament, the patients showed a tendency to prefer the placebo.

In a further test, of 46 in-patients, effective analgesia was obtained in 60 per cent. with aspirin, in 47 per cent. with the placebo, and in 27 per cent. with salicylamide. A statistically significant number of these patients preferred aspirin to salicylamide.

Details are also given of a similar study carried out on 57 patients in which salicylamide, N-acetyl-*p*-aminophenol, and a placebo were compared. The results were similar to those in the first trial. The administration of salicylamide to twenty ambulatory arthritic patients resulted in satisfactory analgesia in only 15 per cent.

In view of these conflicting and surprising results, the authors express doubt about the value of the double-blindfold technique in the assessment of drugs in chronic ailments, suggesting that this method results in a levelling-off of incidence of effectiveness, so that active drugs may be erroneously condemned as ineffective because the same response is obtained with a placebo.

[This challenge to the validity of the double-blind technique in therapeutic trials is important, and the arguments set out in the original paper are worthy of study.] *T. J. Thomson.*

Early Diagnosis and Treatment of Rheumatic Coronary Arteritis. (Ранняя диагностика и лечение ревматических коронаритов) EFIMOVA, G. M. (1955). *Sovetsk. Med.*, **40,** No. 12. 3 figs.

After a brief review of the Russian literature on the subject of coronary involvement and cardiac infarction during the acute stage of rheumatic fever, the author reports from the Sverdiovsk Medical Institute her own

series of thirty cases of "rheumatic coronaritis" in adults. On the basis of the clinical and electrocardiographic (ECG) findings the patients were divided into two categories:

(1) "infarction" (four cases),

(2) "stenocardiac" (coronary insufficiency) (26 cases).

The symptoms and signs in patients in Group 1 were severe precordial pain, tachycardia, moderate fever, leucocytosis, increase in the erythrocyte sedimentation rate, and deep inversion of the T-wave in the ECG.

Symptoms in the patients in Group 2 were less severe, and the ECG showed in some cases inversion of the T-wave and in others a high or low S-T take off.

Treatment with salicylates and amidopyrine is recommended, combined with strict bed rest for a period of 6 weeks for patients in the first group and of 2 to 3 weeks for those in the second.

[The electrocardiograms reproduced represent only four leads, namely, I, II, III, and CR4, and are not convincing.] *A. Swan.*

Influence of an Early Artificial Menopause on Rheumatic Manifestations. (De l'influence d'une ménopause artificielle précoce sur les manifestations rhumatismales.) FORESTIER, J., and DE MARCHIN, P. (1955). *Rev. Rhum.*, **22**, 819.

The authors question the acceptance of the term "menopausal rheumatism" for that chronic type of disease which appears about the age of 50 to 60 and is characterized by arthralgia, paraesthesiae, para-articular and painful "pre-arthrotic" manifestations (excluding the inflammatory types), and which is often attributed to alterations in endocrine balance, especially since oestrogens have been administered with success in these conditions.

The authors then report their observations on two groups of women aged 50 to 60:

(1) Seventy who had suffered early artificial menopause at the average age of 30 and who came under care for chronic rheumatism;

(2) a control group of 200 normal female patients attending the Hôpital de Bavière, Liège, for rheumatism.

Among patients in Group 1 a short interval between the operation and onset of symptoms occurred in only six cases, the average age of onset in the others being 43½ and the average age at the first consultation being 50.

In the control group the average age of natural menopause was 50, at onset of symptoms 46½, and at first consultation 54. Thus the influence of early artificial menopause upon the onset of chronic rheumatism appears to be slight.

Further, among 25 women with artificial menopause before the age of 40, there were six (28 per cent.) with rheumatism, while out of a random group of 100 normal control subjects 26 complained of rheumatism, with or without other disorders.

Among 240 patients at Aix-les-Bains with the type of rheumatism in question, 21 reported onset before the age of 40, but only two of the total 240 had an early menopause, and in neither of these was there early onset of rheumatic symptoms.

The authors conclude that there is little evidence that rheumatic manifestations are due to lack of oestrogens, and suggest that arthralgia and paraesthesiae may be due to neurovegative changes and vasomotor disorders which accompany the menopause, and the rheumatic, pre-arthrotic, and arthrotic lesions chiefly to the degenerative processes of ageing. *V. Reade.*

Use of Reserpine in Psychogenic Rheumatism, Osteo-Arthritis, and Rheumatoid Arthritis. A Preliminary Report. BARTFELD, H. (1955). *J. Amer. med. Ass.*, **159**, 1510. 7 refs.

The action of reserpine in seven cases of psychogenic rheumatism, sixteen of osteo-arthritis, four of rheumatoid arthritis, and three of mixed osteo-arthritis and rheumatoid arthritis was observed at New York University Post-Graduate Medical School. The drug was given in a dosage of 0·1 mg. twice daily, increased to 0·25 mg. twice daily in some cases if there was no response. Of the patients with psychogenic rheumatism five derived benefit—usually less stiffness and muscle pain—from the treatment [but only two are mentioned in any detail]. Of the remaining 23 patients, nine showed some temporary symptomatic improvement [objective changes are not described].

The author concludes that reserpine may help to relieve symptoms in rheumatic disorders and that it should be combined with routine treatment.

K. C. Robinson.

Observations on the Effects of Intra-Articular Phenylbutazone. NEUSTADT, D. H., and STEINBROCKER, O. (1956). *J. Lab. clin. Med.*, **47**, 284. 8 refs.

From the Hospital for Joint Diseases, New York, the authors describe the results obtained with the intra-articular injection of phenylbutazone ("Butazolidin") in the treatment of eighteen patients with rheumatoid arthritis, eleven with osteo-arthritis, and four with allied rheumatic disorders. The drug (1 g. in a 20 per cent. solution containing also lignocaine) was injected at intervals of one to 6 weeks, the usual dose given being 3 to 5 ml. Both the subjective and the objective effects of the treatment were assessed, and in ten cases with effusion weekly aspiration of the synovial fluid was carried out and changes in its cytology noted.

Beneficial results were particularly noticeable in the more acutely inflamed and painful joints with effusion, there being a concurrent decrease in the number of leucocytes in five cases within one to 2 weeks after the injections, while in a few cases in which fluid was aspirated 2½ days after the injection leucocyte disintegration was observed. This effect was similar to the action of phenylbutazone on synovial fluid *in vitro*. Of the eighteen patients with rheumatoid arthritis (who received a total of 45 injections), seven showed major improvement, seven minor improvement, and four no improvement; while of the eleven with osteo-arthritis (receiving 34 injections), marked improvement occurred in only one, slight to moderate improvement was noted in seven, and no improvement in the remaining three.

There was no improvement in four miscellaneous

cases, which included one case each of olecranon bursitis, swollen knee-joint in a patient with ankylosing spondylitis, tenovaginitis of the wrist, and Reiter's syndrome with an acutely swollen knee.

The possible mode of action of phenylbutazone as a specific anti-inflammatory agent is discussed.

H. F. Reichenfeld.

Swellings in the Region of the Second and Third Metacarpophalangeal Joints with Lesions of the Cervical Nerve-roots. (Über Schwellungen in der Umgebung des zweiten und dritten Fingergrundgelenkes bei zervikalen radikulären Reizzuständen.) GENSLER, W. (1955). *Z. Rheumaforsch.*, **14,** 282. 3 figs, 26 refs.

Among 30,000 patients examined at a Hamburg rheumatism clinic during a period of 18 months, swellings confined to the second and third metacarpophalangeal joints were observed in 102 cases, being bilateral in 43. There was thickening of the skin and of the underlying fatty tissue, but no sign of arthritis and no bone changes demonstrable by *x* rays. Pain in the arms and paraesthesiae were common, together with tenderness and limitation of movement of the cervical spine and tenderness in the region of the brachial plexus and of the muscles of the upper arm. There was some weakness of adduction of the fifth finger. Chronic "septic foci" were found in 84 cases. Radiographs of the cervical spine showed degenerative changes and narrowing of the intervertebral foramina. It is suggested that this type of swelling results from a reflex irritation of the spinal roots and must be differentiated from rheumatoid arthritis.

John Lorber.

Vertebral Manipulation. (Les manipulations vertébrales.) DE SÈZE, S., and THIERRY-MIEG, J. (1955). *Rev. Rhum.*, **22,** 633. 10 figs, 5 refs.

Although manipulation of the vertebrae has long been practised by osteopaths it was only about 1944 in France that scientific appraisal of this method of treatment showed that it had a part to play in orthodox medical treatment. In this paper the authors describe the methods adopted at the Hôpital Lariboisière, Paris. They first consider the pathological anatomical changes which in their view are responsible for acute and chronic lumbago and for sciatica, and go on to describe in detail the manipulations necessary to relieve these conditions. They then suggest possible ways in which manipulation can correct the pathological processes affecting the intervertebral disk.

The authors consider that acute lumbago is the lesion most amenable to this form of treatment, as here the pathological condition is reversible, although they add that no guarantee can be given that relapse will not occur. In the treatment of sciatica, however, success was achieved in only 40 per cent. of their cases, largely, they suggest, because in many of these the pathological process had become irreversible; this was the case also in chronic lumbago, in which the results of manipulation were not as uniformly good as in acute lumbago. They state that difficulties arising from this type of treatment are few, provided that the manipulator is expert and that no mistake has been made in diagnosis. In their view vertebral manipulation should not be regarded as a specialty but rather as a part of physical medicine as a whole.

W. Tegner.

Sjögren's Syndrome as a Constitutional Defect. COVERDALE, H. (1955). *N.Z. med. J.*, **54,** 641. 2 tables, 4 refs.

From the pathological changes alone it does not seem to be possible to say with confidence that Sjögren's syndrome is a disease, a part of a generalized tissue abnormality, or an abiotrophy. Any understanding must depend largely on clinical data. In the past this has been obtained from severe cases. A survey of 200 unselected cases, many of them mild, does not support the accepted description of the syndrome in all respects.

Secretion of tears decreases progressively with age. Supposing the glands to be of defective development, the larger number of cases diagnosed at and after middle age could be due to this natural decline of secretion. This series of 200 shows a much greater proportion of young people and males than is usually found and there is evidence that the syndrome is of congenital origin. Different glands and mucous membranes are affected in such a patchy, haphazard way that any central cause seems to be impossible or exceedingly unlikely.

Nature tries to compensate for the lacrimal deficiency by causing the mucous glands of the lids to overact, with the result that blepharitis occurs and there is an excessive secretion of mucus. This is not beneficial. There are other examples of such well-intentioned but useless attempts at compensation. As a first step towards fitting rheumatism into the syndrome a new description of the ocular changes can be given in the following terms:

In the affected eyes there is a defect of lacrimal secretion. This tends to become masked by a compensatory hypersecretion of a different kind which is not necessarily beneficial, and the resulting inflammation may be a product of the defect of secretion or of the compensation or of both. The defect is often, if not usually, present in early life and may be congenital or familial. It varies greatly in degree and tends to cause symptoms of discomfort or distress gradually with the natural aggravation of age, the actual onset being determined by some perhaps trivial incident such as debility, injury, or eye strain. [*Author's Summary.*]

Rheumatism and Ocular Rheumatic Affections. (Sobre el reumatismo y las afecciones reumaticas oculares.) MATA LOPEZ, P. (1955). *Arch. Soc. oftal. hisp.-amer.*, **15,** 1039. 43 refs.

This is a complete and up-to-date review of the ocular manifestations of rheumatism with a detailed description of idiopathic and secondary ocular rheumatism and the different localizations of rheumatism in the eye; it concludes with a discussion on diagnosis and present-day methods of treatment. [Owing to the scope of the paper it cannot be usefully summarized in a short abstract.]

A. Arruga.

Value of Treatment of Reiter's Disease. FOWLER, W., and KNIGHT, G. H. (1956). *Brit. J. vener. Dis.*, **32**, 2. 3 tables, 17 refs.

An assessment of various types of treatment in seventy cases of Reiter's disease, including a miscellany of antibiotics and antihistaminics. The authors found no evidence that any form of therapy at present in use has any influence upon the course of the illness.

P. D. Trevor-Roper.

General Rheumatic Affections and the Eye. (Über Augenerkrankung im Symptomenbilde des Rheumatismus.) MYLIUS, K. (1955). *Z. Rheumaforsch.*, **14**, 222.

In acute rheumatism the eye is almost never affected, but in the chronic form acute or subacute recurrent iridocyclitis is frequent. The author discusses general affections supposed to be of rheumatic aetiology and their ocular symptoms, such as Sjögren's disease, Still-Chauffard's syndrome, scleromalacia perforans, and Reiter's syndrome. *W. Leydhecker.*

Cardiovascular Aspects of Marfan's Syndrome: a Heritable Disorder of Connective Tissue. MCKUSICK, V. A. (1955). *Circulation*, **11**, 321. 17 figs, 3 tables, 76 refs. *J. R. Hudson.*

Origin and Treatment of Rheumatic Manifestations. (Ueber Genese und Therapie des rheumatischen Geschehens.) STORCK, H. (1956). *Med. Klin.*, **51**, 332.

Infection, Allergy, and Pathogenesis of Rheumatic Disease. [In English.] HAGERMAN, G. (1956). *Acta rheum. scand.*, **1**, 209. Bibl.

Rheumatic Diseases in Industry. (Rheumatische Erkrankungen im Industriebetrieb.) BLUMENCRON, W. (1956). *Wien. med. Wschr.*, **106**, 358.

Haemorrhagic Diathesis with Increased Capillary Fragility caused by Salicylate Therapy. FRICK, P. G. (1956). *Amer. J. med. Sci.*, **231**, 402. 16 refs.

Disk Syndrome

Discography in Evaluation of Lumbar Disk Lesions. FRIEDMAN, J., and GOLDNER, M. Z. (1955). *Radiology*, **65**, 653. 3 figs, 8 refs.

The authors present an analysis and critical review of the findings in 150 selected cases of severe back pain of long standing in which discography was performed at Mount Sinai Hospital (University of Minnesota), Minneapolis. In all 150 cases an attempt was made to inject contrast medium into the three lower lumbar disks. Finally a total of 427 disks were injected and examined radiologically, there being only fourteen unsuccessful attempts at injection. In four cases four disks were injected, this occurring where there was a transitional vertebra between the lumbar and sacral segments; the transitional space was injected together with the three disks directly above. In no case was injection of a space above that between L 2 and 3 attempted. [The results are given in tabular form, but there seems to be some confusion in the authors' Table II, where it appears that the columns of figures should be moved one column to the left.]

In fifty of the cases studied myelography with "pantopaque" was also performed. In only fourteen cases did the myelogram and discogram agree completely as to negative or positive findings. In 22 cases they were in complete disagreement; for example, the discogram showed a single offending disk in eleven cases which appeared normal on the myelogram in eight cases, two spaces showing abnormalities on the discogram were normal on the myelogram, while in three cases the discogram showed involvement at three levels whereas the myelogram was completely negative. In the remaining fourteen cases there was partial agreement [these comparative findings are tabulated in detail]. In 32 cases both myelography and discography were performed before operation; the tabulated comparative findings show there was a low rate of agreement between the surgical findings and the myelogram, whereas out of 96 cases operated upon there was full agreement between the surgical findings and those of discography in 88 cases and partial agreement in seven.

It is emphasized that discography was performed only on those patients with long-standing, severe, incapacitating backache for whom surgical intervention was thought to be necessary and in whom the clinical location of the lesion or the results of myelography were inadequate. It is to this selection that the fact that normal findings were so few in this series can be attributed.

J. MacD. Holmes.

Myelography in the Diagnosis of Sciatica. (La mielografía en el diagnóstico de la ciática.) SALVATELLA VIÑALS, J. (1956). *Rev. esp. Reum.*, **6**, 336.

Cervical Traumatic Arthritis. (L'arthrite traumatique cervicale.) PIZON, P. (1956). *Presse méd.*, **64**, 787. 6 figs, 9 refs.

Pararheumatic (Collagen) Diseases

Antimalarials in the Treatment of Discoid Lupus Erythematosus. Special Reference to Amodiaquin (Camoquin.) LEEPER, R. W., and ALLENDE, M. F. (1956). *A.M.A. Arch. Derm.*, **73**, 50. 24 refs.

This paper from the University of California School of Medicine, San Francisco, reports a comparative study of three antimalarial drugs—"quinacrine" (mepacrine), chloroquine, and amodiaquin (camoquin)—in the treatment of a recent series of 32 cases of discoid lupus erythematosus.

Mepacrine was given in a dosage of 0·3 g. daily initially, reduced to 0·2 g. daily when skin discoloration appeared, and maintained at 0·1 g. daily for prolonged treatment.

Of sixteen patients treated with this drug, five improved sufficiently for treatment to be stopped after 3 months (but all had to be re-treated within an average of 3

months), ten showed "encouraging" improvement at first but this was not maintained, and one developed sensitivity to the drug.

Of 29 patients who received one or more courses of chloroquine, starting with 0·5 g. daily for 2 weeks and continuing with 0·25 to 0·5 g. daily, in 22 the condition improved or cleared up entirely (twelve relapsed within one year), in five the rate of improvement was so slow that other measures had to be adopted, the treatment of one was abandoned because of enteritis, and one declined further treatment because of early aggravation of the lesions.

Amodiaquin was given to sixteen patients, most of them receiving 0·2 g. daily; eight of these had previously received both mepacrine and chloroquine, and six chloroquine only. Remission occurred in nine cases although in one this lasted only a month, and considerable improvement was reported in the remainder after 6 months' follow-up. Skin pigmentation did not occur, nor were gastro-enteritis, dyspepsia, blurring of vision, or drug sensitivity reported in any case even where these had occurred during treatment with chloroquine or mepacrine. The commonest side-effect was a feeling of fatigue and lassitude, and only when the daily dose was increased to 0·4 g. did vertigo, weakness, and malaise occur. Tolerance to amodiaquin in general was good, even after 8 months' treatment in one case.

These antimalarial drugs appear to be more effective and safer than treatments previously used in the control of discoid lupus erythematosus. The authors' limited experience with amodiaquin suggests it is similar to chloroquine in effect and that either of these drugs is preferable to mepacrine. *Benjamin Schwartz.*

Pulmonary Manifestations of Generalized Scleroderma (Progressive Systemic Sclerosis.) OPIE, L. H. (1955). *Dis. Chest*, **28**, 665. 8 figs, 25 refs.

The pulmonary changes in generalized scleroderma are described with special reference to twelve cases seen at Groote Schuur Hospital, Cape Town; numerous cases in the literature are also cited.

Pleural involvement is rare in systemic sclerosis, but changes are found in the pulmonary interstitial tissue (pulmosclerosis) and in the pulmonary vasculature. Two main forms of pulmonary infiltration are seen—pulmosclerosis cystica and pulmosclerosis compacta. A third type of pulmonary involvement, which may be a formidable complication of systemic sclerosis, results from secondary broncho-pulmonary bacterial infection or from "spill over" lesions from an accompanying oesophageal stricture. Pulmonary hypertension may also be present, and associated with severe cyanosis, as in one case in the present series. Histological examination may reveal severe pulmonary endarteritis, with which the pulmonary fibrosis combines to accentuate the strain on the right heart. It is emphasized that clinical evaluation of pulmonary hypertension may be difficult in the presence of sclerodermatous changes in the thorax, neck, and arms.

It is recommended that in cases of pulmonary fibrosis or hypertension of uncertain origin a careful search should be made for early dermatological signs, since these may precede florid scleroderma by some years.

J. N. Harris-Jones.

Treatment of Systemic Lupus Erythematosus with Prednisone and Prednisolone. BOLLET, A. J., SEGAL, S., and BUNIM, J. J. (1955). *J. Amer. med. Ass.*, **159**, 1501. 3 figs, 8 refs.

The effect of the new synthetic steroids prednisone and prednisolone was compared with that of older steroids—cortisone, hydrocortisone, or ACTH—in the treatment of cases of systemic lupus erythematosus at the National Institutes of Health, Bethesda, Maryland.

Of the ten patients studied, nine were already receiving hormone therapy but the disease was not satisfactorily controlled. A change was made to prednisone or prednisolone, the dosage of the older steroids being reduced and placebos being given in such a way that the patients were apparently unaware of the change. The initial suppressive daily dose of prednisone was 20 to 60 mg. and the maintenance dose 5 to 30 mg.

It was found that the new synthetic steroids had four times the potency of cortisone, and that the signs and symptoms of acute systemic lupus erythematosus, with some notable exceptions, were suppressed. Renal and cardiac lesions were unaffected, and neither the L.E.-cell phenomenon nor the hyperglobulinaemia was influenced by the treatment. There was little improvement in the mental state or the electroencephalogram in those cases in which abnormalities had been noted before treatment started. There was, however, clearance of pulmonary infiltration in six out of the eight cases in which this had been observed radiologically.

The authors conclude that in general the effectiveness and limitations of prednisone and prednisolone in the treatment of lupus erythematosus closely parallel those of cortisone and corticotrophin, except that the newer steroids do not cause sodium and water retention or potassium loss when administered in moderate therapeutic doses. *J. N. Harris-Jones.*

Lupus Erythematosus. Clinical and Haematological Studies in 77 Cases. MARTEN, R. H., and BLACKBURN, E. K. (1956). *A.M.A. Arch. Derm.*, **73**, 1. 35 refs.

The clinical and haematological features of cases of lupus erythematosus seen in the Sheffield area between 1948 and 1952 are discussed. There were 77 cases during this period, including 66 of chronic discoid, six of generalized discoid, four of subacute disseminated, and one case of acute disseminated lupus erythematosus. The age at onset in the chronic discoid cases varied from 12 to 67 years, with maximum incidence between ages 20 and 44. The condition had been present for less than 10 years in most cases. Except for local trauma in three cases of chronic discoid and exposure to sunlight in one case of subacute disseminated disease there were no specific precipitating factors. Sunlight, however, aggravated the condition in 41 cases of chronic discoid, four of generalized discoid, and two of subacute disseminated lupus erythematosus. In addition to the cutaneous

lesions there were transient joint pains in twelve of the patients in the chronic discoid group, in two patients with generalized disease, and two with the subacute disseminated form. Myalgia was present in two cases of chronic discoid, while in five of the cases in this group there was significant loss of weight. The spleen was palpable in two male patients with chronic discoid lupus erythematosus and there was hepatomegaly in one with generalized discoid disease without other constitutional disturbance.

On haematological examination a microcytic, hypochromic anaemia was found in three females and one male with chronic discoid disease, but there were no cases of haemolytic anaemia. Leucopenia was observed in five and thrombocytopenia in two cases in this group, and in 24 others the erythrocyte sedimentation rate was raised. Also in this group were three cases in which cold agglutinins were present in varying titre and two in which the reaction to the direct Coombs test was positive. L.E. cells were found in the peripheral blood in nine cases of chronic discoid, two of generalized discoid, four of subacute disseminated, and one of acute disseminated disease. In summary, in addition to the expected findings in the subacute and acute cases, some haematological abnormality was found in 36 cases of chronic discoid and five of generalized discoid lupus erythematosus.

These and other published findings are discussed. The authors state that it was not found possible to forecast clinically the cases in which haematological abnormalities might be found, and they conclude that the significance of these abnormalities can only be assessed after prolonged follow up. *Benjamin Schwartz.*

Lupus Erythematosus Profundus. Commentary and Report of Four more Cases. ARNOLD, H. L. (1956). *A.M.A. Arch. Derm.*, **73**, 15. 12 figs, 36 refs.

In lupus erythematosus profundus, a relatively uncommon clinical form of lupus erythematosus, the cutaneous infiltrate occurs primarily in the deeper portion of the corium and gives rise to firm, sharply-defined nodules varying up to several centimetres in diameter lying beneath comparatively normal skin. In this paper the literature is reviewed, particularly reports concerning the association with lupus erythematosus of subcutaneous nodules and plaques usually described as "sarcoid". The author then describes four cases occurring in females in the native population of Hawaii. In three cases the nodules were on the cheeks and in one in the deltoid region.

A summary of the histopathological findings shows the chief characteristics are hyperkeratosis, follicular plugging, epidermal atrophy with loss of rete pegs, oedema of the basal cells, and an infiltrate around the appendages in the corium. Necrobiosis of collagen and fat and fibrinoid alteration of the collagen are also observed.

The differential diagnosis is from Darier-Roussy sarcoid, lupus erythematosus hypertrophicus et profundus in which there are marked epidermal changes, and the Spiegler-Fendt "sarcoid" form of lymphoblastoma. The relationship between the nodules of lupus erythematosus profundus and the transitory nodules occurring in the vicinity of joints in some cases of systemic lupus erythematosus is not clear, but in the reported cases the nodules were persistent and remote from joints, and systemic involvement was not noted.

The paper includes reproductions of photomicrographs obtained in the four cases described.

Benjamin Schwartz.

Ophthalmological Aspects of Periarteritis Nodosa. (Les aspects ophthalmologiques de la périartérite noueuse.) GARCIN, R., MAN, H. X., and GRUNER, J. (1955). *Presse méd.*, **63**, 1792. 8 figs, 1 ref.

This is essentially a case report of a peripheral polyneuritis, specifically a quadriplegia, in a 50-year-old man. By means of muscle biopsy the diagnosis of periarteritis nodosa was made. On initial ophthalmoscopic examination no abnormalities were seen. One month later a single yellowish exudate was seen in the left eye, but again there were no alterations in the vessels. The patient was given ACTH, but in spite of this and other therapy he died one month later. The last ophthalmoscopic examination was made two days before death. At this time there were numerous exudates present, and oedema of the optic nerveheads and retina. Vessels were again essentially normal, and there were only three or four punctate haemorrhages. In the periphery of the right eye there was a single area of exudative detachment; two such areas were seen in the left eye.

Histological examination of the eyes was made and in the retina the vessels showed only a moderate dilatation. However the choroidal vessels showed the characteristic changes of periarteritis. These are beautifully illustrated with coloured photographs. The authors point out that the ophthalmoscopic changes and the anatomical changes in the retina are not specific and only help to corroborate the diagnosis. However the alterations in the choroidal vessels are specific for periarteritis nodosa.

David Shoch.

Physio-Pathology of Collagen Tissue and its Implication in Ophthalmology. (La physio-pathologie du tissu collagène sous l'angle de l'ophtalmologie.) LOMBARD, G. (1956). *Bull. méd.* (*Paris*), **70**, 7. 51 refs.

An interesting general review on collagen tissue: its anatomy, physiology, and chemistry, the part it plays in the healing of infectious and traumatic eye lesions, and therapeutic deductions on the use of cortisone and hyaluronidase in ocular infections and traumatisms.

S. Vallon.

Periarteritis Nodosa Zoster of the Brain with Herpes Zoster Ophthalmicus. (Periarteritis nodosa zosterica des Gehirnes mit Zoster ophthalmicus.) DIETZ, H. (1955). *Nervenarzt*, **26**, 170.

Description of findings at autopsy in a 71-year-old woman with herpes zoster of the ophthalmic region which had caused a periarteritis nodosa of the homolateral side of the brain. *W. Leydhecker.*

Bile as a Suppressive Agent. NAJIB-FARAH (1956). "Proceedings of The Third International Congress of Internal Medicine, Stockholm, September 15-18, 1954", p. 466. Almqvist and Wiksells Boktryckeri AB, Uppsala.

Fresh Ox-Bile percutaneously administered as a Natural and Specific Therapeutic Agent in Rheumatic and Other Affections. NAJIB-FARAH (1956). "Proceedings of The Third International Congress of Internal Medicine, Stockholm, September 15-18, 1954", p. 596. Almqvist and Wiksells Boktryckeri AB, Uppsala.

Non-Articular Rheumatism

Treatment of Lumbago and Sciatica by Vertebral Manipulation. (A propos du traitement des lombalgies et sciatiques par les manipulations vertébrales.) LIÈVRE, J. A. (1955). *Rev. Rhum.*, **22**, 651.

The author discusses critically the results achieved by vertebral manipulation in the treatment of lumbago and sciatica. He agrees that in certain cases this form of treatment is successful, either immediately or gradually after a prolonged course, but points out that it should not be forgotten with regard to the latter type of case that spontaneous remissions occur in both sciatica and lumbago, and also that the development of strong psychological influences between patient and manipulator play their part in helping the patient. He also emphasizes that not all manipulations are successful—in some cases the condition persists in spite of the treatment, and in some even gets worse, and cases of paraplegia, fortunately few, have occurred.

Analysing reports on the success of manipulation, which he does with caution and reserve, the author concludes that this form of treatment is interesting and occasionally sensational, but often only of little value, and on no account should other methods of treatment be abandoned. He considers that the inflammatory factor as well as the purely mechanical one must be borne in mind in considering the aetiology of lumbago and sciatica. His perusal of some American works on cheiropraxis and osteopathy has convinced him that the views on aetiology expressed therein are infantile. Hitherto these methods have been largely in the hands of non-medical practitioners many of whom perform manipulation with great vigour, whereas in fact it should be carried out with the greatest gentleness, and never under a general anaesthetic. The practitioner must be an experienced diagnostician, and should accept only those cases referred to him for manipulation which are suitable for this treatment, for each case must be judged on its merits. The author stresses that manipulation must be a medical technique, and that physiotherapists should be instructed and controlled by medical men. *W. Tegner.*

Ineffectiveness of Splinting in the Treatment of Abductor Paralysis at the Shoulder. SHARRARD, W. J. W., and KNOWELDEN, J. (1956). *Lancet*, **1**, 9. 2 figs, 9 refs.

In a closely argued and well-documented paper the authors question the wisdom of the time-honoured practice of applying an abduction splint in cases of paralysis of the shoulder muscles, and particularly of the deltoid muscle.

An analysis of 359 cases of abductor paralysis in the upper limb from acute poliomyelitis showed that splinting in abduction diminished the recovery of the paralysed deltoid muscle and was of no benefit when the muscle was paretic. Moreover, increased laxity of the shoulder-joint resulted from splinting, while scoliosis was never seen as a result of failure to maintain abduction in cases in which the muscles of the upper limb alone were affected. On the other hand immobilization of the limb by the side in the acute stage of the disease, as is necessary for respirator treatment, produced severe adduction contracture which was avoided in the unsplinted limb by daily passive movement. It is concluded that except in the acute stage and in special circumstances in the convalescent stage of poliomyelitis, splinting of the arm in abduction "is unnecessary and sometimes harmful".

[The authors' argument is well worth studying in the original. One conclusion only, that concerning scoliosis, appears to the abstracter to be less soundly based than the others, as no mention is made of the important part played in causing this deformity by the latissimus dorsi muscle, which is innervated by the same segments as are the shoulder muscles.] *L. Michaelis.*

Radiographic Aspects of Scapulo-Humeral Peri-arthritis. (Aspectos radiográficos de las periartritis escápulo-humerales.) MORENO BLANCO, E., and BOSCH CASAÑS, J. (1956). *Rev. esp. Reum.*, **6**, 298. 16 figs, 11 refs.

General Pathology

Viscosity Studies on Hyaluronic Acid of Synovial Fluid in Rheumatoid Arthritis and Osteo-Arthritis. FLETCHER, E., JACOBS, J. H., and MARKHAM, R. L. (1955). *Clin. Sci.*, **14**, 653. 7 figs, 13 refs.

A detailed study of the viscosity (measured by capillary viscometry) and hyaluronic acid content of synovial fluid is reported from the Royal Free Hospital, London, with special reference to the complexity and polymerization of the hyaluronic acid molecule. Previous assumptions that a higher degree of polymerization exists in the effusions of rheumatoid arthritis than in those of osteo-arthritis were not substantiated.

Values for anomalous viscosity were derived from estimations of specific viscosity under two different degrees of stress at the wall of the capillary as an index of the molecular complexity of the hyaluronic acid molecule. [The formula employed includes a possible source of error in the form of a mean value for the specific viscosity of fluids showing no anomaly.] The limiting viscosity of Sundblad (*Acta Soc. Med. upsalien.*, 1953, **58**, 113) was also determined and his findings confirmed. Hyaluronic acid glucosamine was isolated by Sundblad's method and estimated colorimetrically with Ehrlich's reagent; emphasis is placed on the value of this method in obviating errors due to the interference of proteins and the inconstancy of dried precipitated mucin.

Statistical examination of the mean values obtained for

sixty specimens of effusions from cases of rheumatoid arthritis and twenty from cases of osteo-arthritis suggest that there is:

(1) a similar range of polymer size in the two conditions;

(2) a higher mean value of specific viscosity in osteo-arthritis, which could be explained by a higher concentration of hyaluronic acid in this condition.

Harry Coke.

Serum Globulin Fractions in Chronic Rheumatic Diseases. SALT, H. B. (1956). *Clin. Chem.*, **2**, 35. 18 refs.

Microelectrophoretic separation of the serum globulins was carried out at the Worcester Royal Infirmary in 27 cases of subacute and chronic rheumatic disorders of various types. Those cases in which the serum globulin level was within normal limits (below 3·7 g. per 100 ml.) were separated from those with hyperglobulinaemia and a more detailed study made of the abnormal globulin patterns in the latter group (fourteen cases). The possibility of assay of γ-globulin by a simple salting-out method was also explored.

Statistical analysis showed that there was a significant difference between the two groups in respect of each and every protein fraction. Where the serum globulin level was normal the total protein and albumin levels were also substantially normal, as was that of each globulin fraction. In the hyperglobulinaemic group the total protein level was increased and the albumin level reduced in most cases. The hyperglobulinaemia was most frequently due to an increase in the γ-globulin fraction, often accompanied by an increase in the α_2-globulin fraction. Where electrophoretic analysis showed the serum γ-globulin level to be within normal limits, the figures were in close agreement with those obtained by a salting-out method in which an ammonium-sulphate-sodium-chloride reagent was used; but where the serum γ-globulin level as determined by electrophoresis was increased, the salting-out technique gave results which were significantly lower. That this may have been due to heterogeneity of the proteins was suggested by the presence of split peaks in the electrophoretic patterns.

[No reference is made to the relationship between these changes and the clinical type of rheumatic disorder or the duration or phase of the rheumatic process—factors to which other authors have ascribed an influence on the levels of the individual globulin elements. The salting-out process is not related to other more usual chemical methods of estimating γ-globulins.] *Harry Coke.*

Blood Picture and Bone-Marrow Findings in Rheumatic Diseases. (Blutbild- und Knochenmark-befunde bei rheumatischen Krankheiten.) SEIDEL, K., and SCHMIDT, G. (1956). *Münch. med. Wschr.*, **98**, 224. 17 refs.

Antistreptolysin-O Reaction in Normal Subjects and in Various Pathological Conditions. (La reazione dell' anti-O-streptolisina in soggetti normali ed in diverse condizioni patologiche.) INZERILLO, R., AZZENA, D., and MAZZUCCO, C. (1955). *Arch. "Maragliano" Patol. Clin.*, **2**, 785. 40 refs.

Value of Agglutination Reactions with Erythrocytes sensitized with an Immune Serum in Chronic Inflammatory Rheumatism. (Valeur des réactions d'agglutination des globules rouges sensibilisés par un immunsérum au cours des rhumatismes inflammatoires chroniques.) JACQUELINE, F., EYQUEM, A., and JOCHEM, E. (1956). *Rev. Rhum.*, **23**, 115. 32 refs.

Histamine-Eosinophil Test in Rheumatoid Arthritis and Rheumatic Fever. [In English.] KALLIOMAKI, L. (1956). *Acta rheum. scand.*, **1**, 235. 1 fig., 8 refs.

Diagnostic Significance of Acute Phase Protein in Synovial Exudates. Preliminary Report. [In English.] CARLSON, F. S. (1956). *Acta rheum. scand.*, **1**, 267. 18 refs.

Observations on a Precipitin Reaction between Serum of Patients with Rheumatoid Arthritis and a Preparation (Cohn Fraction II) of Human Gamma Globulin. EPSTEIN, W., JOHNSON, A., and RAGAN, C. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 235. 5 refs.

ACTH, Cortisone, and Other Steroids

Preliminary Clinical and Laboratory Trials with Prednisone (Δ^1-Dehydrocortisone) Administered by the Intra-Articular Route. (Prime esperienze cliniche e di laboratorio con il prednisone (Δ^1-deidrocortisone) somministrato per via intra-articolare.) ROBECCHI, A., CARTESEGNA, F., and DANEO, V. (1955). *Reumatismo*, **7**, 337.

The authors report the results of the intra-articular injection of prednisone in twenty cases of chronic arthritis (eleven of rheumatoid arthritis) and compare them with those obtained with hydrocortisone. From their experience in this small number of cases observed over a short period only it would appear that the clinical effect of 5 mg. prednisone is rather less than that of 25 mg. hydrocortisone. With larger doses (10 to 25 mg.), however, prednisone is more effective. No ill-effects were noted. *L. Michaelis.*

Hydrocortisone in Painful Shoulder. A Controlled Trial. MURNAGHAN, G. F., and MCINTOSH, D. (1955). *Lancet*, **2**, 798. 6 refs.

At the Royal Infirmary, Edinburgh, the authors compared the results of treatment with local injections of hydrocortisone in 24 cases of painful shoulder with those obtained with injections of lignocaine ("xylocaine") in 27 similar cases. Active exercises were also prescribed in both groups, which were comparable in respect of age incidence (chiefly 46 to 65 years) and sex distribution. Cases of old or recent bone injury, of complete rupture of the supraspinatus tendon, and of painless stiff shoulder were excluded from the trial, which was confined to patients with a functional disability resulting from what "would generally be accepted as periarthritis". All injections were made into the periarticular tissues and directed especially at areas of localized tenderness. A volume of 5 ml. was injected, containing either 25 mg.

hydrocortisone acetate or 2 per cent. lignocaine, 1,000 units of hyaluronidase being added in each case. A clinical assessment of the severity of the pain and the degree of limitation of movement (abduction and external rotation) was made before treatment and repeated at weekly intervals after treatment for 3 or 4 weeks and less frequently thereafter. Pain was assessed by the same observer throughout and evaluated according to a numerical scale based on various subjective and objective factors.

Significant improvement was noted in both groups. The average reduction in pain was the same after each type of injection, being most marked after one week and diminishing slightly after 8 to 12 weeks. The improvement in abduction was greater after one week in the group treated with hydrocortisone (average increase of 15 degrees, compared with 6 degrees in the group treated with lignocaine), but was approximately equal in the two groups at 8 to 12 weeks (16 and 18 degrees respectively). The improvement in external rotation paralleled that observed in abduction. (In no case was there any significant initial limitation of flexion or extension.) The greatest over-all improvement was obtained in those cases in both groups in which treatment was given within 10 weeks of the onset of the disability. Where the duration of the disability was 1 to 5 weeks the two drugs were equally effective, but results were better with lignocaine when it was 6 to 10 weeks, and with hydrocortisone when the disability was of longer standing. A history of trauma made no difference to the degree of improvement obtained. Both groups contained some instances [numbers not specified] of dramatic improvement and some of no improvement whatsoever. In one case severe anaphylaxis developed towards the end of an injection of hydrocortisone and lasted 5 minutes; the authors ascribe this to injection into a vein.

[The authors apparently assume that the pain and functional disability are purely periarticular in origin in these cases, as injection into the joint itself was avoided.]

M. Kendal.

Cortisone and Corticotropin Treatment of Pemphigus. Experience with 28 Cases over a Period of Five Years. NELSON, C. T., and BRODEY, M. (1955). *A.M.A. Arch. Derm.*, **72**, 495. 1 fig., 7 refs.

At the Presbyterian Hospital (Columbia University), New York, 27 patients with pemphigus vulgaris and one with pemphigus foliaceus (in all cases confirmed by biopsy) received steroid treatment and were followed up for 5 years. It was found that a combination of 25 mg. corticotrophin (ACTH) given intravenously over 6 to 8 hours followed by 300 mg. (initially) cortisone by mouth daily gave the quickest control of the symptoms; when this was achieved ACTH in a gelatin menstruum, given intramuscularly every 24 to 72 hours, was substituted. Later still, oral cortisone was usually sufficient to maintain the patient and every effort was made to reduce the dosage as soon as possible.

Of the 28 patients, 21 were still alive 5 years after the start of treatment, and only two of these were bedridden. It was found that once control of the symptoms was achieved, there was progressively less need for the hormones, and indeed one patient has been free from symptoms for 25 months without any form of treatment. Of the seven deaths, five were thought to be due to inadequate doses of hormone; the other two patients died after thrombo-embolic episodes. Side-effects were numerous, as would be expected with the prolonged and high dosage employed, but in no case was it necessary to discontinue the treatment. *G. W. Csonka.*

Indirect Analysis of Corticosteroids. III. Determination of Steroidal Dihydroxyacetones. NORYMBERSKI, J. K., and STUBBS, R. D. (1956). *Biochem. J.*, **64**, 168.

The 17-ketogenic steroids (17-KGS) comprise three structural sub-groups: the 17:20-diols, the 17:20:21-triols, and the steroidal dihydroxyacetones (SDHA). It was found that compounds belonging to the last subgroup react with metallic zinc to give products which are no longer 17-ketogenic. A method was developed for the differentiation of 17-KGS in the urine, wherein the urine is treated with zinc powder in the presence of acetic acid and then with sodium bismuthate: the formed 17-ketosteroids (determined as Zimmermann chromogens) provide a measure of their precursors, *i.e.* of zinc-resistant 17-KGS (diols and triols) and indirectly also a measure of zinc-labile 17-KGS (SDHA).

It was found that in normal men and women the ratio of urinary SDHA to 17-KGS varied between 20 and 60 per cent., in rheumatoid arthritic patients receiving cortisone or ACTH it varied between 40 and 80 per cent., in the last trimester of pregnancy it varied between 10–30 per cent., and in the adrenogenital syndrome the ratio was less than 10 per cent.—[*Author's Summary.*]

Indirect Analysis of Corticosteroids. IV. A Note on the Role of Chloride and Urea in the Bismuthate Treatment of Urines. NORYMBERSKI, J. K., and STUBBS, R. D. (1956). *Biochem. J.*, **64**, 176.

In view of Smith and Tompsett's recent publication (*Analyst*, 1955, **80**, 397) concerning the non-specific oxidizing properties of sodium bismuthate in the presence of the chloride ion, the question was examined whether urinary chloride does interfere with the determination of 17-hydroxycorticosteroids or their subgroups by any of the methods employing the treatment of the urine with sodium bismuthate. No such interference could be demonstrated—a finding which was rationalized by the observation that urea effectively inhibits the non-specific action of bismuthate/chloride.—[*Authors' Summary.*]

Clinical Use of "Fludrocortisone" Acetate. Preliminary Report. HAMWI, G. J., and GOLDBERG, R. F. (1955). *J. Amer. med. Ass.*, **159**, 1598. 6 figs, 1 ref.

This preliminary report from Ohio State University, Columbus, describes the effects of "Fludrocortisone" (9-α-fluoro hydrocortisone) acetate on twelve patients with various disorders.

An improvement in the mental state and a gain in weight (partly due to fluid retention) were produced in a patient suffering from anorexia nervosa. Suppression of the excretion of 17-ketosteroids and 17-hydroxy-

steroids was achieved in a case of adrenal virilism. Sodium retention and negative potassium, nitrogen, calcium, and phosphorus balances were observed in a 20-year-old woman with an exacerbation of chronic choroiditis; progressive improvement in the choroiditis was noted while the patient was receiving the drug.

"Fludrocortisone" provided satisfactory replacement therapy during and after total or subtotal adrenalectomy in two cases (in one of which, however, sudden hypotension following a transfusion reaction necessitated the giving of additional fluid). No increase in urinary 17-hydroxysteroids occurred after adrenalectomy, so that fludrocortisone may be given in cases of acute adrenal insufficiency without impairing the diagnostic significance of this estimation. In six cases of Addison's disease small doses of fludrocortisone acetate (averaging 0·5 mg. every 2 to 3 days) proved adequate for replacement purposes. Overtreatment caused rapid sodium retention and weight gain. *Denis Abelson.*

Clinical and Metabolic Effects of Prednisone. NABARRO, J. D. N., STEWART, J. S., and WALKER, G. (1955). *Lancet*, **2**, 993. 20 refs.

From the Middlesex Hospital, London, the authors report their experience with prednisone in the treatment of five cases of lymphatic leukaemia, one case of malignant lymphoma, and one of Henoch-Schönlein purpura, the dosage being 1/5 to 1/3 that of cortisone for which prednisone was substituted; in a further case of Hodgkin's disease prednisone was given from the start of treatment. In order to compare the effects of cortisone, hydrocortisone, prednisone, and 9-α-fluoro hydrocortisone, metabolic studies were also carried out on two patients receiving substitution therapy following total adrenalectomy and on one healthy male subject.

All the cases are briefly described. Clinical control of the neoplastic process with a concomitant rise in the haemoglobin level to normal or near-normal was achieved for varying periods.

In the first seven cases troublesome side-effects from cortisone had become manifest; of these, only oedema and sodium retention were beneficially influenced by prednisone. This finding that prednisone had much less effect on sodium metabolism than cortisone was borne out by the results of balance studies.

One patient in the series relapsed and died from a severe urinary infection some 4 weeks after beginning treatment.

An initial potassium diuresis was observed in the healthy subject, in the patient with Hodgkin's disease, and in one of the patients receiving prednisone in substitution for cortisone.

Creatinine output was not affected by prednisone, but the urinary excretion of nitrogen was slightly increased in those patients in whom there was potassium diuresis.

In one case the results of insulin-tolerance tests carried out during cortisone therapy were similar to those of similar tests performed 2 weeks after prednisone had replaced cortisone.

Diabetes developed in two cases during administration of prednisone.

The absolute eosinophil count, which was determined in the healthy subject and the two patients treated after adrenalectomy, indicated that prednisone was three to five times more potent than cortisone in depressing the number of eosinophils.

The authors, in conclusion, emphasize that only the least serious of the complications of steroid therapy—namely, sodium retention—is prevented by the use of prednisone, and that the most serious—fulminating infections, osteoporosis, steroid diabetes, peptic ulceration, and mental changes—are just as likely to develop with prednisone as with cortisone. *H. F. Reichenfeld.*

Use of Hydrocortisone by Local Injection. KENDALL, P. H. (1956). *Ann. phys. Med.*, **3**, 1. 1 fig., 15 refs.

The author reports the results obtained at Guy's Hospital in the treatment of 512 patients with joint and soft-tissue lesions by the topical injection of hydrocortisone. Affected joints were injected with 1 to 2 ml. hydrocortisone (25 to 50 mg.) plus 1,000 units hyaluronidase, but in the case of soft-tissue lesions 1 to 3ml. 2 per cent. procaine was substituted for the hyaluronidase in order to locate the lesion accurately and to give relief until the effect of the cortisone developed. Injections into tender areas around the shoulder joint were accompanied by injections into:

(1) the joint capsule,
(2) the subacromial bursa,
(3) the long head of biceps.

Of 121 cases of rheumatoid arthritis, 75 per cent. showed "dramatic improvement" in symptoms and signs (plus increased range of movement) within 24 to 36 hours, such improvement lasting 7 to 10 days after each injection. The author considers the most suitable cases to be:

(*a*) those in which one or two joints are primarily affected,

(*b*) those in which polyarticular affections have responded to general treatment with the exception of one or two joints,

(*c*) those in which cortisone or other drug therapy is being gradually withdrawn.

In 36 cases of bilateral static osteo-arthritis of the knee, however, the degree of improvement was no better than that in 36 control cases treated only with 2 per cent. procaine. On the other hand 41 cases of active inflammation (that is, those with minimal radiological changes in the joint or with aggravation of the osteo-arthritis by injury) gave "far better results".

Of 61 cases of acute periarthritis of the shoulder, 45 were completely relieved of symptoms and thirteen improved within 7 to 14 days of injection.

Of 23 cases of chronic periarthritis (showing chiefly fibrosis and impaired mobility), thirteen recovered completely with the help of active assisted exercises in addition to the injections, in 4 to 6 weeks.

Relief was also obtained in a high proportion of cases of traumatic synovitis (with or without haemarthrosis), tennis elbow, golfer's elbow, plantar fasciitis, De Quervain's syndrome, tenosynovitis, and traumatic arthritis of the elbow-joint.

Among the side-effects noted were a transient local urticaria (three cases), local inflammation (two cases), and a relatively mild, spontaneously-resolving, suppurative arthritis of the knee-joint. The author ascribes improvement in the acute cases to an "anti-inflammatory" effect, and tentatively suggests that improvement in chronic cases (for example, "frozen shoulder", "trigger finger") may be due to a fibrinolytic action. He states that the main value of hydrocortisone treatment in some of the above conditions is not so much in curing them as in appreciably hastening recovery—the principal aim of those concerned in rehabilitation. *M. Kendal.*

Inflammatory Rheumatism and Prolonged Treatment with Prednisone. (Rhumatismes inflammatoires et traitements prolongés par la prednisone.) DE SÈZE, S., DEBEYRE, N., and BORDIER, P. (1956). *Bull. Soc. méd. Hôp. Paris*, **72**, 216. 1 ref.

The authors report the results obtained during a period of one year with prednisone in the treatment of 91 cases of rheumatoid arthritis and 91 cases of ankylosing spondylitis.

In 28 cases in which no previous treatment with adrenocortical hormones had been given the response proved spectacular, 27 of these patients being able to resume a practically normal life taking a daily maintenance dose of 5 to 15 mg.

In 57 cases the symptoms were already adequately controlled by maintenance therapy with cortisone or hydrocortisone, but in most of them further improvement was noted after changing to prednisone—certain residual inflammatory foci subsided and there was a concurrent fall in the erythrocyte sedimentation rate.

The remaining fifteen patients, who were receiving cortisone but had responded poorly, improved slightly when prednisone was substituted.

The reports of previous workers regarding the absence of side-effects with prednisone were not confirmed, the present authors finding the same precautions and strict medical supervision to be necessary as with cortisone. "Moon-face" developed in 55 cases, and observations on two patients suggested that this was likely to result from any relaxation of the salt-free diet, even when the dose of prednisone was only of the order of 10 mg. daily. Generalized capillary vasodilatation leading to erythema was noted in 45 cases, acne in four, increased capillary fragility in fifteen, and hypertension in 26. Psychic disturbances—especially insomnia—tachycardia, and over-excitability were repeatedly noticed, as were hyperglycaemia and gastric disturbances.

H. F. Reichenfeld.

Adrenal Cortical Function in Hypothermia. EGDAHL, R. H., NELSON, D. H., and HUME, D. M. (1955). *Surg. Gynec. Obstet.*, **101**, 715. 3 figs, 6 refs.

This paper from the U.S. Naval Medical Research Institute, Bethesda, Maryland, describes investigations into the adrenal cortical reaction pattern during hypothermia and rewarming in mongrel dogs anaesthetized with sodium pentobarbitone or thiopentone and ether. Blood was obtained from the right adrenal vein by means of a cannula and repeated estimations of the 17-hydroxycorticosteroid content made. Hypothermia was produced by:

(1) exposure to an external temperature of −10° C.;

(2) cooling the blood in an external arteriovenous shunt with ice water at 4° C.;

(3) total immersion in ice water at 4° C.

Rewarming was accomplished by immersion in water at 45° C. At all temperatures below 30° C. positive pressure respiration was instituted.

During hypothermia produced by any method in eleven dogs 17-hydroxycorticosteroid secretion was reduced; it recovered on rewarming, rising above the control level in about half the dogs. Constant infusion of ACTH (corticotrophin) during hypothermia in ten dogs made no difference to this fall in secretion, nor did maintenance of the blood pressure at a constant level in two dogs by infusion of noradrenaline. The blood ACTH level was estimated during hypothermia in two dogs and was found to be reduced. In further experiments cold was applied locally to one adrenal gland in two dogs, a normal body temperature being otherwise maintained. A significant fall in corticoid production was noted, with a rapid return to normal on rewarming.

The authors state that it appears likely that in hypothermia there is a depression of ACTH secretion and adrenal corticoid output and also of tissue uptake, so that there is no relative deficiency of the hormones in the tissues. The immediate return of secretion to normal on rewarming indicates that the adrenal gland is not damaged by hypothermia. *B. L. Finer.*

Some Aspects of the Physiological Effects of Cortisone in the Treatment of Pemphigus Vulgaris. NEILL, J. (1955). *Brit. J. Derm.*, **67**, 434. 3 figs, 16 refs.

In order to illustrate the different effects of ACTH and cortisone in an individual case the author presents from the Victoria Infirmary, Glasgow, the detailed case report of a woman aged 54 who had suffered from pemphigus vulgaris for 2½ years and who was treated for 2 years with cortisone or ACTH.

The first course of treatment, with 100 units ACTH daily for 13 days, 75 units for one week, 50 units for one day, and 25 units for 3 days, resulted in a partial remission of the condition, followed by an immediate relapse on withdrawal of the hormone after 25 days owing to shortage of supplies. Cortisone (150 mg. daily) was then given and kept the patient free from lesions but, because adrenal depression was feared, 80 units of ACTH gel were substituted for the cortisone and an immediate relapse followed. She was then treated with both ACTH and cortisone, and once more there was a remission. In all, four courses of ACTH were given, each resulting in a relapse which was only ended by further administration of cortisone.

An estimation of adrenal function was made, based on the excretion of 17-ketosteroids. Evidence that there is adrenocortical damage in pemphigus vulgaris is presented and it is suggested that, as a result, treatment with ACTH is unreliable. Adrenal depression from cortisone treatment is thought to be much greater than is generally appreciated, and a sudden change from

cortisone to ACTH is likely to be followed by a relapse, or even by adrenal failure if the disease has been present for a long time. Thus a "boosting" course of ACTH to maintain the adrenocortical secretion is a risky procedure.

It is concluded, therefore, that cortisone is the drug of choice in the treatment of pemphigus vulgaris.

S. T. Anning.

Chemical Studies on Synovial Fluid relative to Intra-Articular Injection of Hydrocortisone Acetate. DAL-CORTIVO, L., PATTERSON, M. B., and UMBERGER, C. J. (1955). *J. Lab. Med.*, **46**, 720. 5 figs, 2 refs.

In order to study the behaviour of hydrocortisone on injection into the knee joint, fluid was aspirated 2, 3, 5, 10, 15, and 30 minutes (and in some cases at longer intervals) after the injection of 50 or 75 mg. in a number of cases at the Hospital for Special Surgery, New York.

The amount of hydrocortisone in each specimen was then estimated quantitatively by an ultraviolet spectrophotometric method. [The number of subjects studied and the condition of the joints injected are not specified.]

It was found that in cases where a good clinical response resulted, the concentration of hydrocortisone in the synovial fluid diminished rapidly, starting within a few minutes of injection. This suggests to the authors that the loss of hydrocortisone from the joint does not result from simple diffusion across the synovial membrane.

Oswald Savage.

Biological Effects of Aldosterone with Especial Reference to Man. PRUNTY, F. T. G., MCSWINEY, R. R., and MILLS, I. H. (1955). *Proc. roy. Soc. Med.*, **48**, 629. 2 figs, 15 refs.

The therapeutic effects of aldosterone, particularly in Addison's disease, are discussed. In one case of Addison's disease the metabolic changes and weight loss which followed complete withdrawal of conventional treatment were reversed by administration of aldosterone in a dosage of 200 μg. daily for 3 days followed by 400 μg. daily for 2 days. During the 5 days' treatment there was no noticeable effect on pigmentation or blood pressure. Sodium and chloride retention occurred, but sodium was retained in excess of the chloride, suggesting the possibility of intracellular transfer of sodium. Potassium balance was not affected, but there was a more positive water balance and even a slight increase in weight. In a girl with adrenal hyperplasia leading to pseudohermaphroditism who received more than double the dosage of aldosterone given to the first patient similar results were obtained, except that there was a significant change in potassium balance, involving rebound retention. Nitrogen excretion was not increased in either of these two cases. Aldosterone was found to be most effective when given by intramuscular injection, less effective when given by intravenous infusion, and least effective by mouth.

In another case of Addison's disease 225 μg. aldosterone intravenously resulted in sodium retention which was a little less than that produced by 5 mg. DCA (deoxycortone acetate). The latter drug had less effect on potassium excretion than aldosterone.

In all the cases there was definite evidence of water retention in response to aldosterone. The eosinophil count, the fasting blood sugar level, and insulin tolerance were uninfluenced by the drug.

P. A. Nasmyth.

Metabolic Response to Total Adrenalectomy and Hypophysectomy. MASON, A. S. (1955). *Lancet*, **2**, 632. 7 figs, 11 refs.

The metabolism of patients after adrenalectomy or hypophysectomy in the treatment of carcinomatosis was studied at the London Hospital to determine whether the characteristic postoperative responses—sodium retention, potassium loss, and nitrogen loss with subsequent regain—occur in the absence of the pituitary or the adrenal glands. Balance studies were carried out on eight patients with carcinoma of the breast, two of whom had undergone total hypophysectomy, one total adrenalectomy, and five both total adrenalectomy and oophorectomy. In the two cases of total hypophysectomy normal postoperative response was obtained when substitution therapy with a constant daily dosage of corticotrophin was given. Similarly, in the remaining patients the metabolic response was normal so long as the daily dosage of cortisone was maintained.

These results in the human subject thus confirm the experimental findings of Ingle (*J. Endocr.*, 1951, **8**, 23) that postoperative metabolic changes do not depend solely on alterations in adrenocortical activity.

C. L. Cope.

Eleven Cases of Oedematous Exophthalmos treated with ACTH, Cortisone, and Hydrocortisone. (Sur onze cas d'exophthalmie oedémateuse traités par la corticostimuline (ACTH), la cortisone, et l'hydrocortisone.) DECOURT, J., DOUMIC, J.-M., and MICHARD, J.-P. (1954). *Ann. Endocr. (Paris)*, **15**, 733.

In the cases reported three patients were given cortisone only, five ACTH only, and three cortisone and ACTH in sequence, with the addition of hydrocortisone in one. ACTH was the most effective. There was regression in four patients and marked improvement in the oculomotor disturbances in two. The effect is rapid and transitory.

M. H. T. Yuille.

Course of Parenchymatous Keratitis treated by Local Cortisone. [In Czech.] KUBISTOVA, V. (1955). *Csl. Ofthal.*, **11**, 323. 11 refs.

A favourable response is reported in thirteen out of fourteen patients treated.

M. Klima.

Acute Corneal Lesions caused by Cortisone. (Lesioni corneali acute da cortisone.) DA POZZO, E. (1954). *Atti 40 Cong. Soc. oftal. ital., 1953*, **14**, 262. 4 refs.

Extensive disjunction of the corneal epithelium was observed after local treatment with cortisone for a superficial punctate keratitis of probable herpetic origin.

S. Magni.

Metabolites of Hydrocortisone and Cortisone in Synovial Fluid in Rheumatoid Arthritis. WILSON, H., FAIRBANKS, R., SCIALABBA, D., MCEWEN, C., and ZIFF, M. (1956). *J. clin. Endocr.*, **16**, 86. 5 figs, 35 refs.

Comparative Studies of the Clinical Activity of Hydrocortisone in Relation to that of Prednisone. (Estudios comparativos sobre la actividad clinica de la hidrocortisona con relacion a la prednisone.) RUIZ MORENO, A. (1955). *Arch. argent. Reum.*, **18,** 95.

Treatment of Lumbago and Neuralgia with Subarachnoid Hydrocortisone. (Le traitement des lombalgies et des névralgies par l'hydrocortisone sous-arachnoïdienne.) LIÉVRE, J. A., ATTALI, P., GAUTIER, J. C., and MICHEL, J. (1955). *Rev. Rhum.*, **22,** 671.

Prednisone and Prednisolone as Therapeutic Agents. Progress Report on their Integration into General Medical Practice. SPIES, T. D., STONE, R. E., GARCÍA LÓPEZ, G., DÍAZ TELLECHEA, C. M., LÓPEZ TOGA, A., REBOREDO, A., and SUÁREZ, R. M. (1955). *J. Amer. med. Ass.*, **159,** 645. 8 figs, 2 refs.

Clinical and Laboratory Studies of Chronic Arthritis treated by Intra-Articular Injections of Delta-Dehydrohydrocortisone (Prednisolone). (Ricerche cliniche e di laboratorio su artropatici cronici sottoposti a iniezione intra-articolare di deltadeidro-idrocortisone (Prednisolone)). ROBECCHI, A., DANEO, V., and CARTESEGNA, F. (1956). *Reumatismo*, **8,** 1.

Hydrocortisone Acetate Injected Locally. (L'acetate d'hydrocortisone en injections locales.) WEISMANN-NETTER, R., KREWER, B., and LORCH, P. (1955). *Rev. argent. Reum.*, **20,** 147.

Observations on the Regulatory Mechanisms of Aldosterone Secretion in Man. BECK, J. C., DYRENFURTH, I., GIROUD, C., and VENNING, E. H. (1955). *Arch. intern. Med.*, **96,** 463. 4 figs, 12 refs.

Value of Hormone Therapy in the Rheumatic Diseases. BOLLET, A. J. (1956). *J. Mich. med. Soc.*, **55,** 278 and 302 12 refs.

Personal Experience in the Treatment of Rheumatic Disorders with Δ^1-Dehydrocortisone (Prednisone, Metacortandracin). (Experiencia personal en el tratamiento de las enfermedades reumáticas con la Δ^1-dehidrocortisona (prednisona, metacortandracina.) BARCELÓ, P., and SANTAMARÍA, A. (1956). *Rev. esp. Reum.*, **6,** 281. 17 refs.

Avoidance of Reactions to Local Hydrocortisone. (Cómo evitar las reacciones de la hidrocortisona local.) SÀNS SOLÁ, L., and BARCELÓ, P. (1956). *Rev. esp. Reum.*, **6,** 293. 13 refs.

Other General Subjects

History of Osteopsathyrosis (Osteogenesis Imperfecta). (Die Geschichte der Osteopsathyrosis (Osteogenesis imperfecta).) VALENTIN, B. (1955). *Centaurus (Kbh.)*, **4,** 132. 7 figs, bibl.

Osteopsathyrosis (osteogenesis imperfecta) is widespread throughout the world and has been recognized for over 200 years, though of the numerous articles on the disease in the medical literature, few contain anything but case reports. Looser pointed out in 1906 that the intrauterine and postnatal forms of the disease were identical in origin, and this is generally agreed. More recently Cocchi has gone a step further and claimed that three types of the disease can be identified—foetal osteogenesis imperfecta (Vrolik), osteopsathyrosis (Lobstein) (with two subtypes), and the triad of hereditary fragilitas osseum (blue skin, deafness, and fragility). The disease is due to a disturbance of bone development, and in particular of new bone formation. There is no failure of calcification, but a disturbance of the bone-forming elements, possibly with increased bone absorption. As a result there is reduced resistance to bending stresses, which results in fractures from trivial causes.

The first report of a case, published in 1674 by Nicholas Malebranche, was that of an idiot child who had multiple fractures of the limbs "such as a criminal suffers after being broken on the wheel", and the condition was attributed to the mother having witnessed such an event during her pregnancy. The same view was taken of many subsequent cases, even those reported by Buffon (1707–88). The first published illustration of a case is of an 8-month foetus described by Bordernave (1728–82) before the Academy of Science in Paris in 1763. The first suggestion that the condition was of constitutional origin was made in 1788 by Ekmann in a thesis published in Uppsala. With the spread of scientific knowledge, the descriptions of cases published after this date were much more complete and accurate, and began to include details of the post-mortem examination. A familial tendency was first detected by Strack in 1806, who described the delayed onset of the disease in three brothers, one of whom, Edmund Axmann, subsequently became a doctor. In 1831 Axmann described changes in the sclera which he had observed in himself and his brothers, and first pointed out that this was characteristic of the syndrome, although his observation went unnoticed by subsequent authors.

In the second volume of his *Traité d'Anatomie Pathologique*, published in 1833, Lobstein first clearly distinguished the disease under the name of "osteopsathyrosis idiopathica" and used the expression *casser comme du verse* to emphasize the exceptional fragility of the bones. Even so, other authors continued to attribute the condition to foetal rickets and later to infantile osteomalacia. More accurate observations were made by Vrolik (1801–63) who finally differentiated the disease from rickets and gave it the name of "osteogenesis imperfecta", which has since been more generally used than the earlier name of osteopsathyrosis. Fragility of the bones was the only feature generally recognized until blueness of the sclerotics was reported afresh as a new observation in 1896, in 1900, and again in 1913. The third characteristic feature, deafness, was first mentioned by Dighton in 1912. Ekmann had already emphasized the striking enlargement of the skull in 1788, while a further sign, the general laxity of the joints which has often led to recurrent dislocation, was mentioned by Axmann.

Amongst the well-known persons who have suffered from the disease may be mentioned Honoré de Balzac, whose blue sclerotics were described by Gautier, and Henri de Toulouse-Lautrec. *J. G. Bonnin.*

Ann. rheum. Dis. (1956), **15**, 295.

GROWTH IN STILL'S DISEASE

BY

B. M. ANSELL AND E. G. L. BYWATERS

From the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, Bucks, and the

Department of Medicine, Postgraduate Medical School, London

(RECEIVED FOR PUBLICATION SEPTEMBER 28, 1956)

The factors governing normal growth in man are complex and their inter-relationships need clarification. Much of our knowledge is based on assumptions derived from experiments in other species: in man observation of the modification of growth by disease and its treatment has been the only direct mode of inquiry. Such diseases may be classified as:

(*a*) general disturbance of a long-lasting nature, *e.g.* congenital heart disease (Adams and Forsyth, 1951; Campbell and Reynolds, 1949; Lund, 1952), diabetes mellitus (Bogan, 1940; Beal, 1948; Hernberg and Heikel, 1951), allergic disorders (Cohen, Weller, and Cohen, 1940; Cohen and Abram, 1948; Welsh, 1951), bronchiectasis (Findlay and Graham, 1927), blood diseases such as primary polycythaemia (Halbertsma, 1933), and congenital haemolytic anaemia (Langston, 1935), chronic renal disease (Ellis and Evans, 1933), or the sequel to atomic explosions (Greulich, Crismon, and Turner, 1953).

(*b*) local disturbances of nutrition, metabolism and function, *e.g.* joint tuberculosis (Gill, 1944; Sissons, 1952), osteomyelitis, angioma, poliomyelitis (Harris, 1930), infantile hemiplegia or post-encephalitic Parkinsonism (Gaunt, 1949).

(*c*) Certain endocrine and metabolic diseases specifically affect bone growth throughout the body, *e.g.* hypothyroidism, rickets (either primary or secondary), and pituitary disorders.

Rheumatoid arthritis in children or Still's disease offers a favourable opportunity of studying the inter-relationship of these various factors in growth, since not only is there a local disturbance of growth due to nearby joint disease but there is also a general disturbance of metabolism. Furthermore, the picture may be modified by the effects of treatment, which again may act on the body as a whole or by suppression of local inflammation.

Material

We have, therefore, undertaken a survey of the general growth and bone development in 119 children suffering from Still's disease seen at this unit within the period 1948-1953, in whom the disease started before the age of 14. The age and sex distribution of this group (Fig. 1, overleaf) corresponds with that in the largest series hitherto published (Coss and Boots, 1946; Edström, 1947; Sury, 1952). It should be pointed out, however, that in contrast to other series, such as those of Coss and Boots (1946) and Barkin (1952), many children were referred here in the early stages of their disease.

This series is selected only by reference to hospital and by the exclusion of four children in whom the diagnosis was not beyond doubt at the time when this analysis was begun. Within the group of 119, height and weight data were not analysed in three cases in whom the disease had commenced before the age of 5 years, and in fifteen cases with onset between 5 and 14 years, either because of associated disease (asthma, oesophageal stricture, and congenital heart disease: three cases) or because of inadequate records (fifteen cases).

The wrist and hand *x* rays were examined in all cases, as well as *x* rays of other joints, as indicated clinically. Radiographs from three additional subjects, diagnosed after the conclusion of the study, are also used for illustration.

All patients were treated with a good general diet, physiotherapy, adequate rest, splintage, analgesics, iron, and blood transfusion where necessary. Six patients were treated in addition with methyl testosterone 25 mg./day by mouth for one or two 6-week periods, and data on a further case treated thus, not in this series because her disease commenced at 15 years, are also surveyed. Twelve patients who were seen within 9 months of the onset of the disease were treated with oral cortisone acetate in sufficient quantity to suppress symptoms (the dose varying from 25-150 mg./day) and continued thus as long as disease activity was thought to be present. No case was treated for less than 3 months and most of these patients received continuous hormone for at least one year. Six more patients received hormone therapy in a similar way, but in these cases the

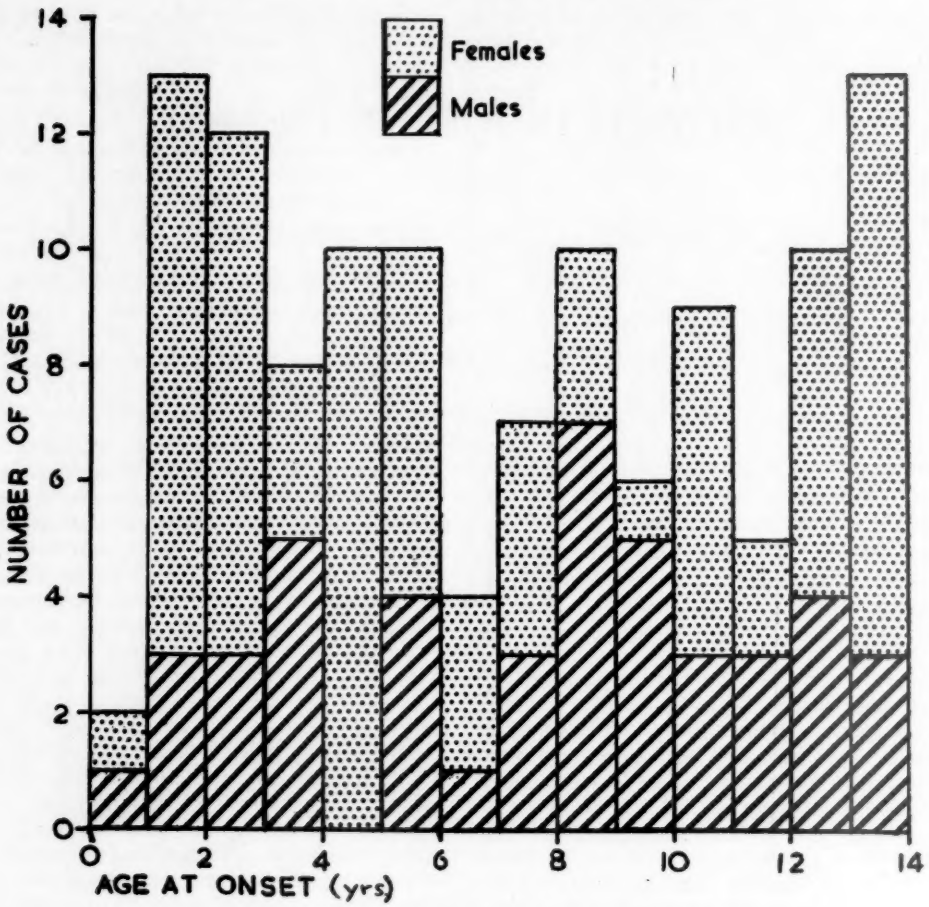


Fig. 1.—Age at onset and sex distribution of 119 cases of Still's disease.

use of the drug was begun considerably later in the course of the disease. Once any form of hormone therapy was started, subsequent data were considered separately as part of the hormone-treated group. The remaining 95 patients were treated conservatively as indicated above.

Methods

Height and weight were measured when the patient was first seen, during hospital treatment, and at regular intervals after discharge. The heights were taken standing, since recumbent measures were found to be inaccurate, sometimes showing differences of several inches. In cases with flexion deformities of the hips and/or knees, the heights were not used for comparison. *X* rays were taken of both hands and wrists on entry, at intervals during the stay in hospital, and at the annual follow-up examinations. For the purpose of analysis these *x* rays were considered in three groups:

(1) Those patients in whom there was no clinical evidence of wrist involvement at any time,
(2) Those who had shown clinical involvement of the hand or wrist for a period of 3 months or less (and had then returned to normal),
(3) Those in whom the hand or wrist joints had been involved continuously for more then 3 months.

The measurements of height, weight, and skeletal development selected for analysis were those taken at the patient's first and subsequent annual visits.

Assessment of growth in weight and height has been by comparison with a mean normal range established by Holt and McIntosh (1941) for 0-5 years and that given by the Ministry of Health for schoolchildren aged 5-14 years (Menzies, 1940), the results being expressed as a percentage above or below this mean standard level. It is recognized that these standards are relative and that adjustments may be needed for comparison with present day populations. Indeed, while this analysis was in progress, a further report was made by the London County Council (Daley, 1950) which suggests that London schoolchildren are now 3 in. taller and 2 lb. heavier than at the previous survey 10 years earlier. Because of this the heights and weights of sixty children

between the ages of 5 and 14 years admitted to hospital within one month of the onset of a first attack of rheumatic fever were analysed in the same way. Only two of these showed weights more than 10 per cent. below the standard as defined above, and none showed height or weight more than 10 per cent. above standard. It was therefore felt that a deviation of 10 per cent. from this standard could be taken as abnormal.

The points noted in the radiographs were the presence of prematurity or retardation in epiphyseal development, the state of epiphyseal fusion, and metaphyseal growth lines and growth defects, as well as abnormal periosteal growth and erosions due directly to the disease. Skeletal maturity estimations were all made by one of us (B.A.) by reference to the standards of Greulich and Pyle (1950). Each radiograph was assessed blind (only the sex of the child being known) and, on two separate occasions, the interval between readings varying from 6 to 12 weeks. Firstly the development of the epiphyses as a whole was judged to be equal to, in advance of, or behind the standard by one year and changes in single epiphyses were then examined more closely. The figures obtained were later compared and correlated with the actual age of the child. In only two out of 449 radiographs was there a marked discrepancy between the separate readings. Mainland (1953), discussing the use of skeletal age as a means of estimating development, suggested that there was considerable systematic and variable error. The probable reason for our apparently smaller variable error is due to the fact that we did not attempt to estimate the small changes occurring in periods of less than one year. No estimate of systematic error was made. All the radiographs were reviewed by both of us to minimize errors in the assessment of abnormalities due to the disease process.

Correlation was made with the presence of disease activity as judged by clinical signs and with an erythrocyte sedimentation rate raised above an upper limit of 15 mm./hr (Westergren) at the time of assessment.

Results

(1) Growth as Weight (Table I).—No child was more than 10 per cent. above standard weight when first seen and only four out of a total of 76 treated conservatively became so during the period of observation. Each of these four children had shown no disease activity for at least one year before the overweight measurement. Conversely, loss of weight early in the disease was common; 21 out of 53 were more than 10 per cent. below the standard when first seen within one year of the onset. Weight rose with recovery, and, in many instances, particularly where the disease was of fairly short duration (1-3 yrs), it returned to normal. The minimum weight recorded was 50 per cent. of the standard normal, but in the majority of cases it was between 60 and 70 per cent. of normal in the 5 to 14 age group and between 70 and 80 per cent. in the under 5 group.

TABLE I

CORRELATION OF WEIGHT DEFECT WITH DURATION AND ACTIVITY OF DISEASE IN CHILDREN ON CONSERVATIVE THERAPY*

Time since Onset (yrs)	Proportion of Patients more than 10 per cent. below Normal				Total Number in One Year
	Under 5 years old at Onset (42 cases)		Between 5 and 14 years old at Onset (59 cases)		
	Active	Inactive	Active	Inactive	
0–1	7/19	0/0	14/34	0/0	53
1–2	6/10	1/6	12/20	2/6	42
2–3	1/2	3/12	10/14	2/10	38
3–4	4/9	0/7	10/13	0/5	32
4–5	3/5	3/7	3/4	1/3	19
5–10	8/10	2/7	11/11	1/5	33

* Each case figures once only in each year-since-onset group, but only 53 of a total of 101 cases furnished readings for the first year. There was a total of 217 readings for the 101 cases.

(2) Growth as Height (Table II).—It can be seen that height is much less frequently affected than weight. Here again duration of activity appeared to be an important factor in the production of this defect, since when the disease became inactive the height returned to normal in the course of 2 to 3 years

TABLE II

CORRELATION OF HEIGHT DEFECT WITH DURATION AND ACTIVITY OF DISEASE IN CHILDREN ON CONSERVATIVE THERAPY*

Time since Onset (yrs)	Proportion of Patients more than 10 per cent. below Normal				Total Number in One Year
	Under 5 years old at Onset (42 cases)		Between 5 and 14 years old at Onset (59 cases)		
	Active	Inactive	Active	Inactive	
0–1	3/17	0/0	0/29	0/0	46
1–2	2/11	0/6	2/13	0/9	39
2–3	0/3	1/11	3/10	0/10	34
3–4	1/7	0/8	1/7	0/7	29
4–5	1/5	0/7	0/2	0/3	17
5–10	3/9	0/7	4/7	1/2	25

* Each case figures once only in each year-since-onset group, but only 46 of a total of 94 cases furnished readings for the first year. There was a total of 190 readings for the 94 cases.

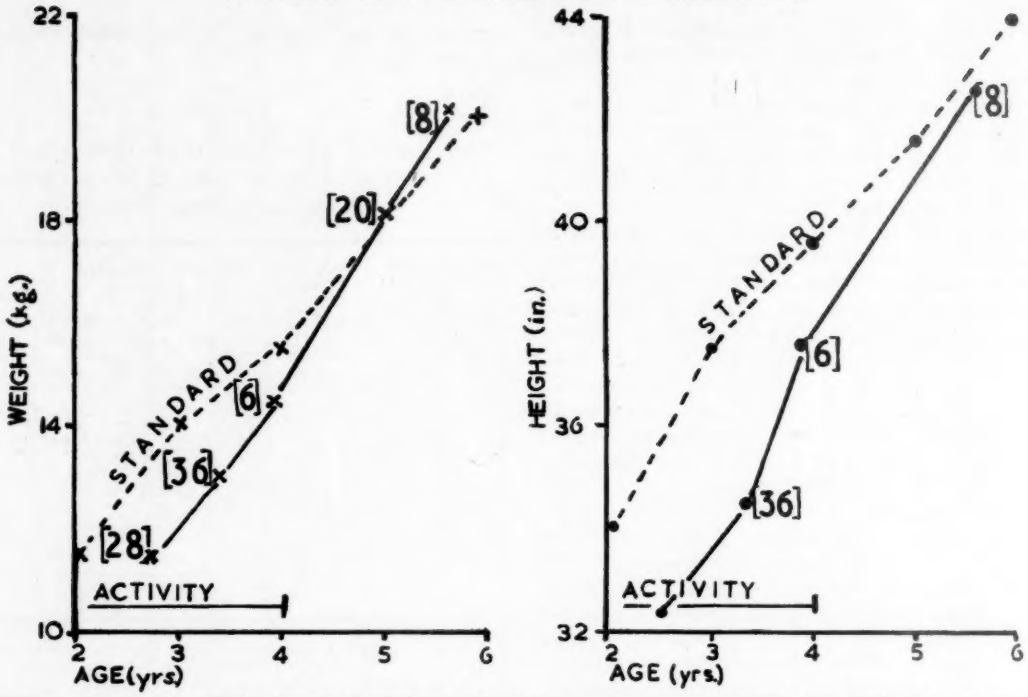


Fig. 2.—Height and weight of a girl with rheumatoid arthritis starting at 1½ years of age compared with a standard curve. As the activity of the disease regressed (see erythrocyte sedimentation rate figures at each point) both height and weight rose towards normal.

provided there had been no premature fusion of epiphyses (Fig. 2). The minimum height recorded in this series was 80 per cent. of normal; those patients in which this defect persisted as the disease became inactive were of very long standing and had had the disease severely. As we did not include the height data of those seriously affected children in whom there were flexion deformities of the hips and knees, these results are perhaps less striking than they otherwise might be, since these are the cases most likely to have defective bone growth. That severe disease alone can produce height defect is shown in Fig. 3 (opposite), and that this is more pronounced when there is much resultant joint deformity is shown in Fig. 4 (opposite).

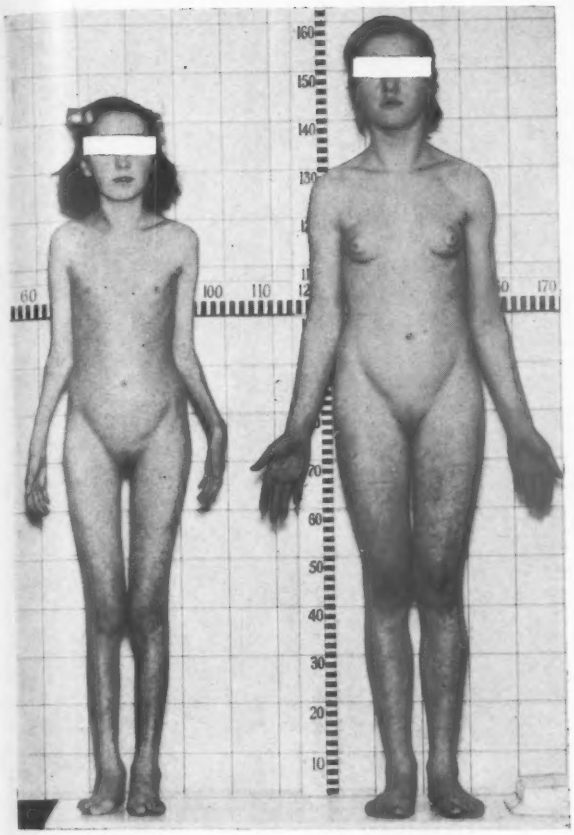
(3) *X*-Ray Analysis

(*a*) *Epiphyseal Development and Fusion.*—In Group I (with no involvement of the wrist at any time) there were eight patients under 5 years of age: a total of 27 radiographs of the hands and wrists covering the first 10 years of the disease were studied (the odd number is due to a patient with one normal and one affected wrist). In one case, both wrists showed a general retardation of the carpal epiphyses. In four cases there was retardation of a single epiphysis, the ulnar styloid (bilateral in three); in two of these this was followed by advancement of this epiphysis when the disease became quiescent, the others all remaining normal for the age. Growth lines were present in the radius in seven *x* rays of four cases and these four were the same who had shown the growth abnormality of the ulna.

In the 5 to 14-year age group, a total of 66 radiographs of eighteen cases with neither wrist involved and four cases with only one normal wrist were examined. In six cases (fourteen radiographs) retardation of development affected more than one epiphysis. In four of these cases showing general retardation the other wrist was clinically severely affected, but its development was normal or in advance of the age. Growth lines were observed in 21 of the 66 normal radiographs and involved nine cases (50 per cent.), three of these showing no retardation of epiphyseal development.

To compare the effect of another long-continued illness on skeletal development, hands and wrists were analysed from nine children between the ages of 3 and 14 years who were suffering from rheumatic fever, which had been continuously active for at least 6 months before the *x* ray was taken. In twelve of the radiographs (both hands of six patients), growth lines were present. Only one showed a year's retardation, involving a single epiphysis (ulnar).

In Group II (patients who had shown wrist involvement for less than 3 months) a total of six cases under 5 years (sixteen radiographs), and seven



Patient Normal

Fig. 3.—Twin sisters aged 14, one normal (height 61½ in., weight 47·2 kg.) and one after 5 years of moderately active rheumatoid arthritis (height 55½ in., weight 26·8 kg.).

patients between 5 and 14 years (thirty radiographs) were examined over the 10-year period following the onset of the disease. In the under 5-year age group, two cases (six radiographs) showed general sub-normal development, two other cases (four radiographs) had growth lines, and one case (two radiographs) had abnormal periosteal elevation. In the older age group, three patients (seven radiographs) showed retarded development, and in one case both wrists showed advancement of ulnar epiphyseal growth. Four cases (seven radiographs) showed growth lines: three having retarded development, and the fourth growth lines on one side and abnormal periosteal accretion on the other.

As was expected, the majority of changes occurred in Group III (*i.e.* in those cases in which wrist involvement continued for more than 3 months). A total of 31 (129 radiographs) of the under-5s and 49 (181 radiographs) in the 5 to 14s were reviewed. In the under-5s (Table III, overleaf), a tendency to acceleration of epiphyseal development was noted

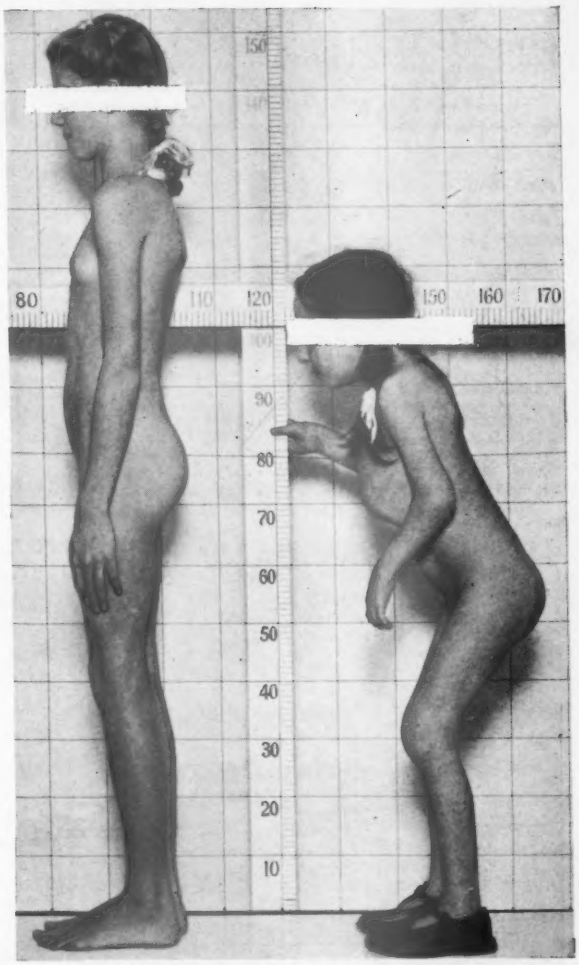


Fig. 4.—Two children aged 11 years, one normal and one with rheumatoid arthritis of 5 years' duration showing severe deformities as well as stunting.

in fifteen cases (37 radiographs), while ten cases (29 radiographs) showed retardation and three cases (five radiographs) showed a mixture of retardation and acceleration. As might be expected, premature epiphyseal fusion was rare early, but tended to occur later, causing growth defects particularly after 4 years of illness. This decrease usually affected the ulna and occasionally the metacarpal bones.

In the 5 to 14-year age group (Table III, overleaf) acceleration of epiphyseal development occurred in fourteen cases (32 radiographs), retardation in eighteen cases (37 radiographs), and a mixture of the two in two cases (three radiographs). The tendency to premature epiphyseal fusion occurred earlier in the course of the disease as the age of the patient increased, so that this was noted even as early as the second year of the illness. Premature fusion may also occur in involved joints in an affected

TABLE III

ANALYSIS OF 312 RADIOGRAPHS OF HANDS AND WRISTS OF EIGHTY CASES WITH BILATERAL INVOLVEMENT FOR MORE THAN 3 MONTHS, SEEN BETWEEN 0 AND 10 YEARS SINCE ONSET OF DISEASE

Number and Type of Cases in which Abnormalities were seen

Age at Onset (yrs)		0–5		5–14	
Total Number of Cases		31		49	
Side		Right	Left	Right	Left
Epiphyseal and Carpal Development	Normal	5	6	21	21
	Advanced	14	15	14	14
	Retarded	10	9	13	12
	Mixed	2	3	1	2
Premature Epiphyseal Fusion		3	2	15	17
Growth Defects		9	10	17	18
Growth Lines		23	24	26	25
Periostitis		17	16	15	19
Erosions		18	18	32	30

hand; Fig. 5 shows a case with severe involvement of one carpus and wrist only, in which the epiphyses of all terminal phalanges fused more than 2 years before the uninvolved side.

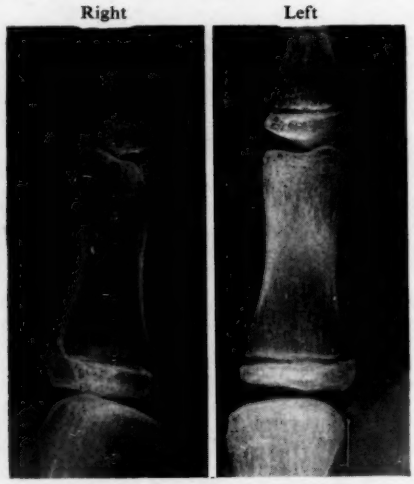


Fig. 5.—Radiographs showing epiphyseal fusion in unaffected thumb joints on the side of a right wrist affected for 3 years, compared with the thumb of the contra-lateral normal hand in a boy aged 16.

(*b*) *Growth Defects.**—Because of the tendency to premature fusion, growth defects occurred earlier and more frequently in the older than in the younger patients. Eighteen cases showing defects were noted in the older age group (5-14 years at onset), being unilateral in six (38 radiographs); the younger group (0-5 years at onset) included ten cases showing defects. Most of these occurred in the ulna and the 4th and 5th metacarpal bones, although occasionally the phalanges were affected (Fig. 6). Despite the many growth defects seen radiologically, obvious clinical deformities (such as that seen in Fig. 7) were rare, occurring in only five children.

* Deficiency in linear growth of bones compared with opposite or neighbouring bones.

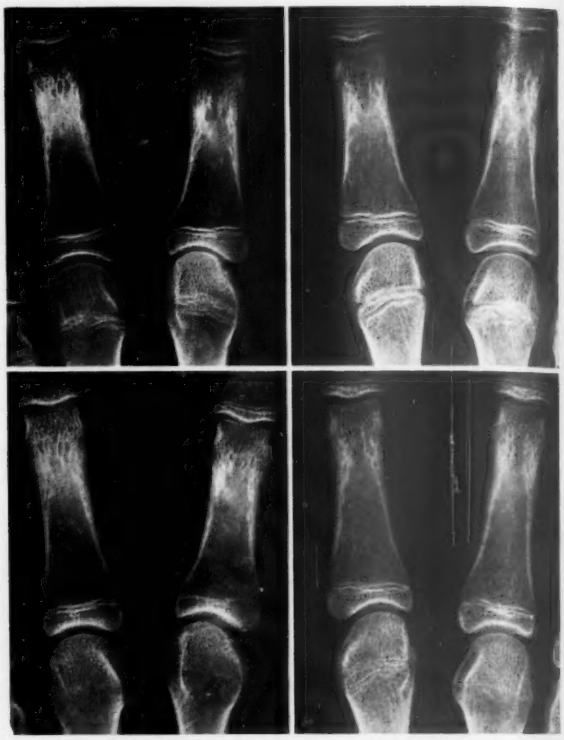


Fig. 6.—Premature fusion of epiphyses in the neighbourhood of the involved second right metacarpal and third right proximal interphalangeal joints at 14 and 28 months, in a boy who was 14 years old at the onset of disease. The right second metacarpal grew 1 mm. in this period and the left grew 3 mm.

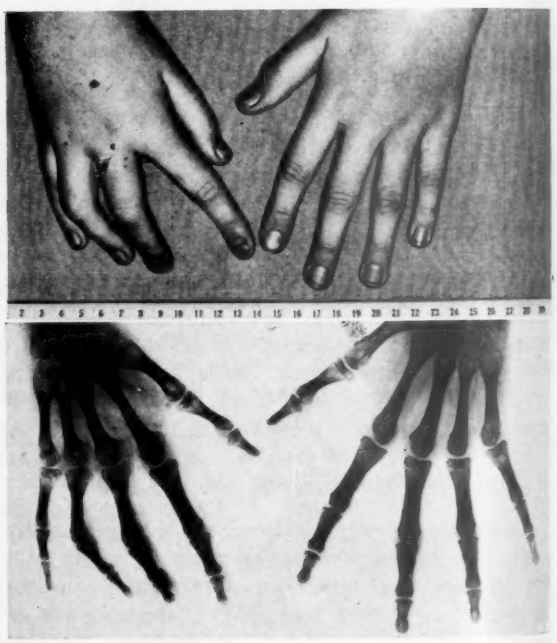


Fig. 7.—16 per cent. shortening of right third and fourth metacarpal bones in a girl aged 13 who had had rheumatoid arthritis for 11½ years.

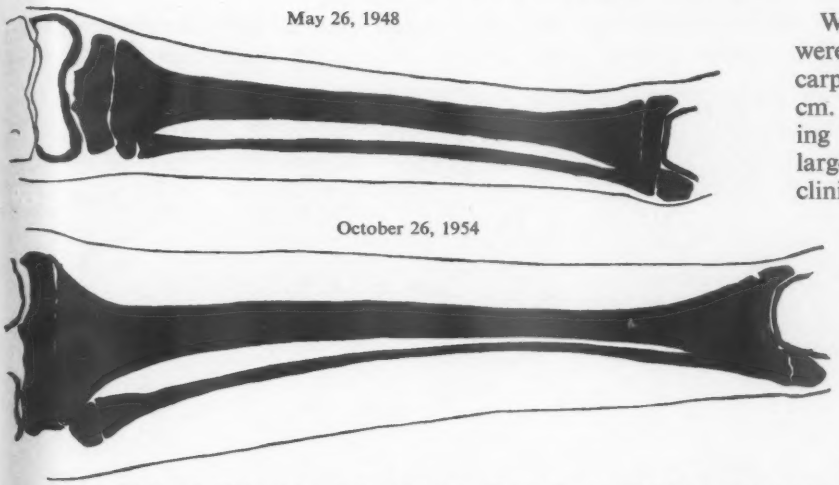


Fig. 8.—Rheumatoid arthritis involving the knee joint, starting at the age of 5¾ years; *x*-ray tracing shows increased bowing of the fibula between the ages of 7 and 13 years.

Where unilateral growth defects were present, the affected metacarpal was between 0·4 and 1·3 cm. shorter than the corresponding healthy one, but only the larger defects were obvious on clinical inspection. In the forearms and legs where two bones may be differentially affected by growth disturbances, gross deformities may sometimes occur. Recognition of this in the early stages (Fig. 8) is important from the point of view of orthopaedic management, since the gross deformities seen in Fig. 9 may thus be avoidable.

Fig. 9.—Gross clinical deformity of the legs previously diagnosed as rickets in a girl of 13 years who had had rheumatoid arthritis since the age of 1½ years. Lateral and antero-posterior radiographs show the fibula bowing in relation to the epiphyseal development of the tibia at the involved knee and ankle joints.

The very minor degrees of growth inhibition manifest as growth lines were often pronounced. These developed in the epiphyses as well as in the metaphyses, producing a double-contoured effect (Fig. 10).

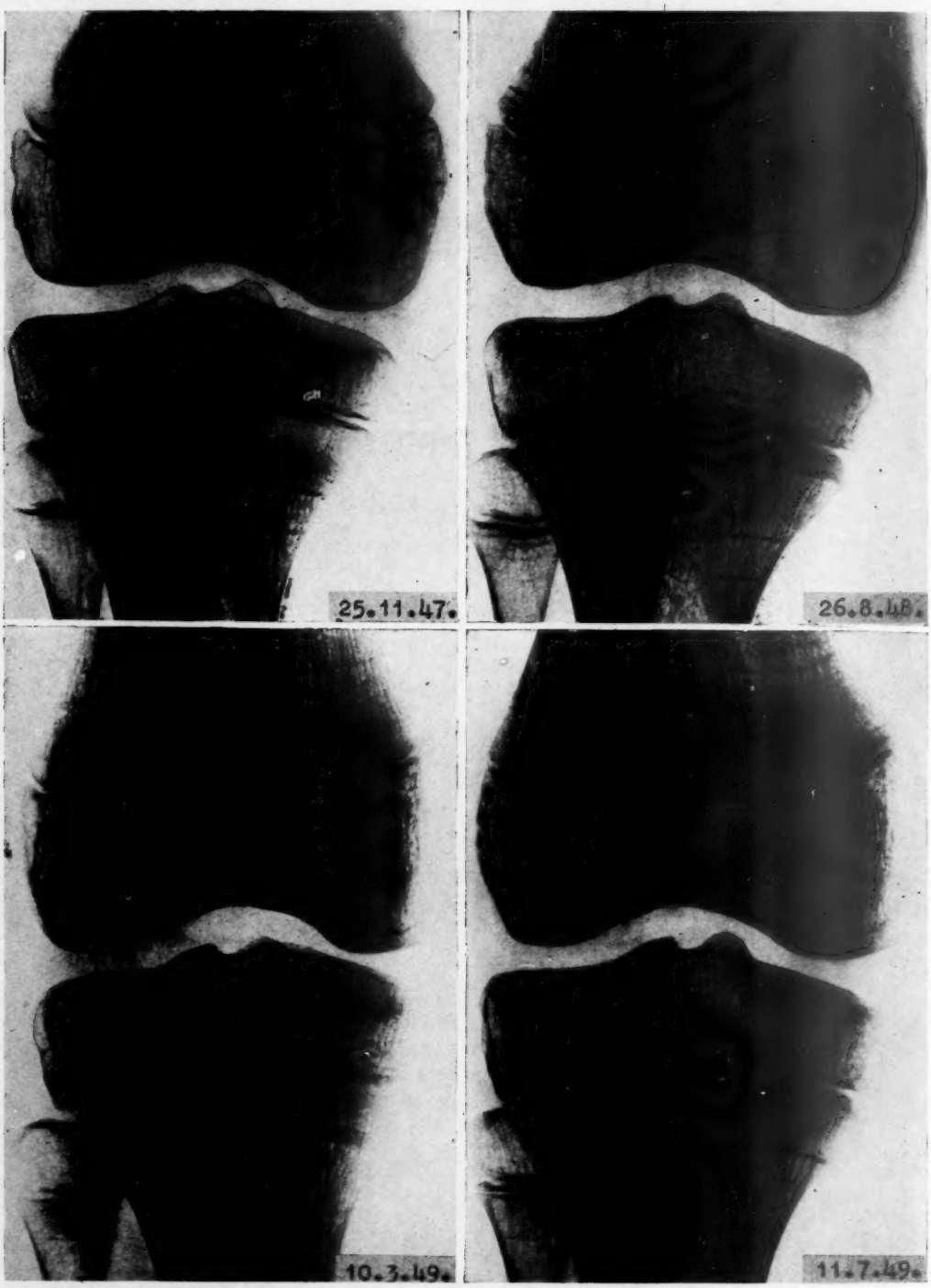


Fig. 10.—Development of double contours round femoral and tibial epiphyses over a period of 1½ years in a boy bedridden for 3 years from the onset of the disease at the age of 8½ years. This is due to dense recalcification of rarefied areas seen in the first *x* ray, at the age of 12, after mobilization, resulting in the metaphysis in a dense growth line well seen in the last two *x* rays.

Histologically this is seen to be produced by a well-marked transverse bony layer separated from subchondral bone (Fig. 11).

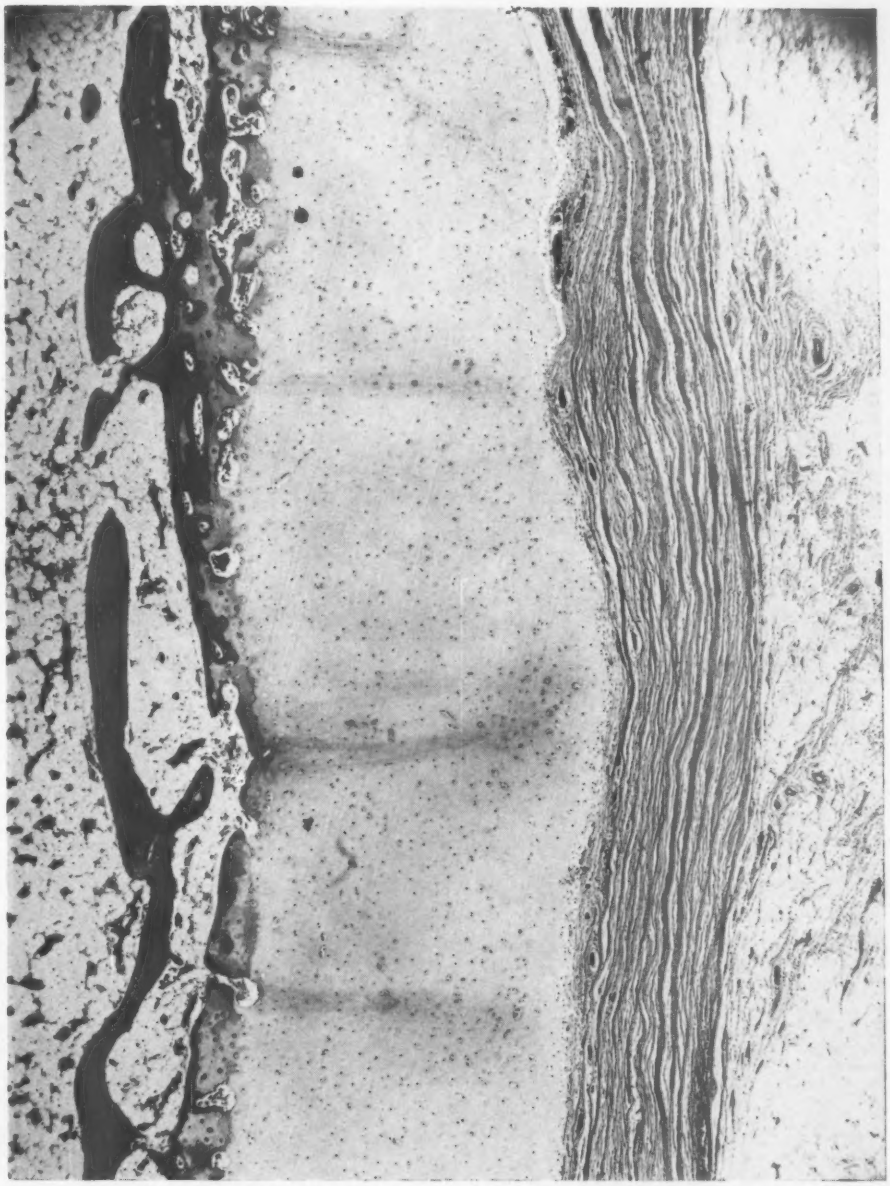


Fig. 11.—Photomicrograph of the femoral condyle (haematoxylin and eosin × 25) in girl aged 13, showing surface pannus and double-contoured bone lines.

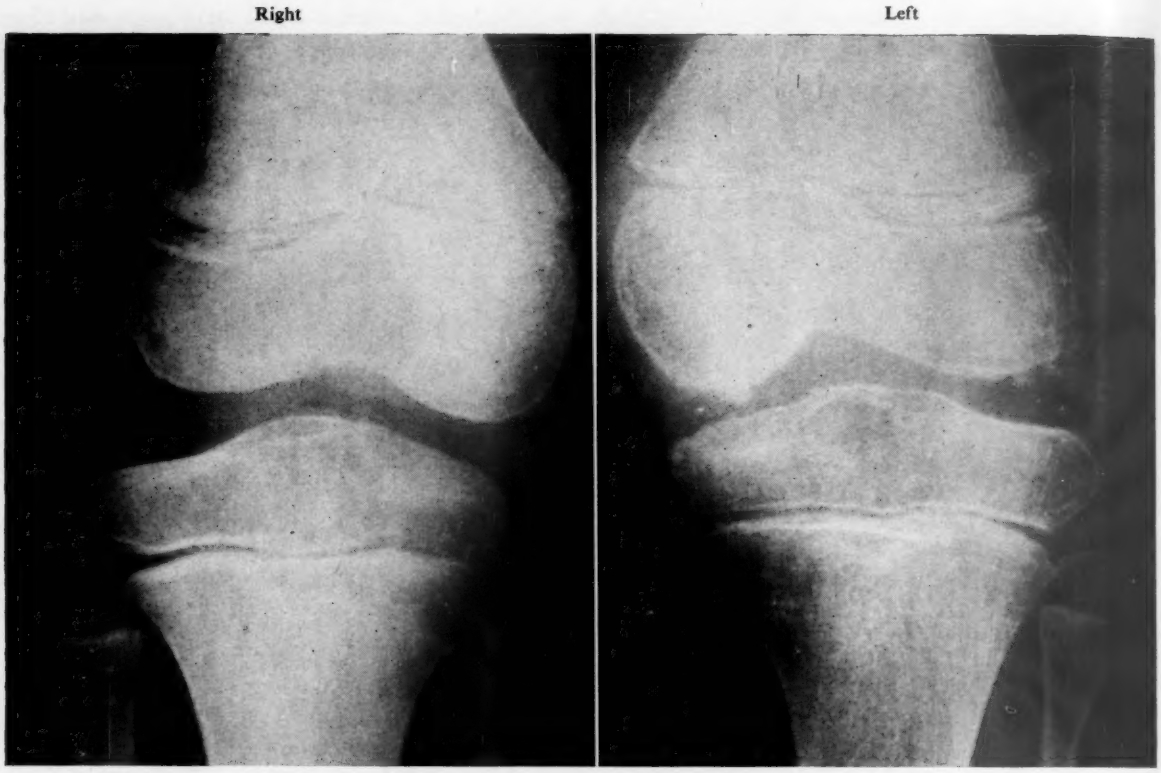


Fig. 12.—"Woolly" subchondral bony outgrowths developing in the affected knee compared with the normal side in a boy aged 8½ at the onset of rheumatoid arthritis. Radiographs taken 18 months after onset.

This did not seem to be related to the woolly subchondral bony outgrowths seen at early ages, which are more pronounced in Still's disease and on the affected side (Fig. 12).

Fig. 13.—Photomicrograph (haematoxylin and eosin × 40) showing vascular outgrowths from the lower femoral epiphysis in a child aged 3½ who had had severe rheumatoid arthritis for 2½ years, showing slight variable calcification in portions of the periphery.

The latter is due to irregular outgrowths of vessels into cartilage and subsequent ossification (Fig. 13).

Whilst most of the severely affected patients suffered general stunting and showed generalized growth lines, there might be either stimulation or retardation of growth in the neighbourhood of inflamed joints. This might affect either epiphyseal or metaphyseal growth. In a child with only one knee joint affected there was a marked increase in epiphyseal size on the affected side (Fig. 14).

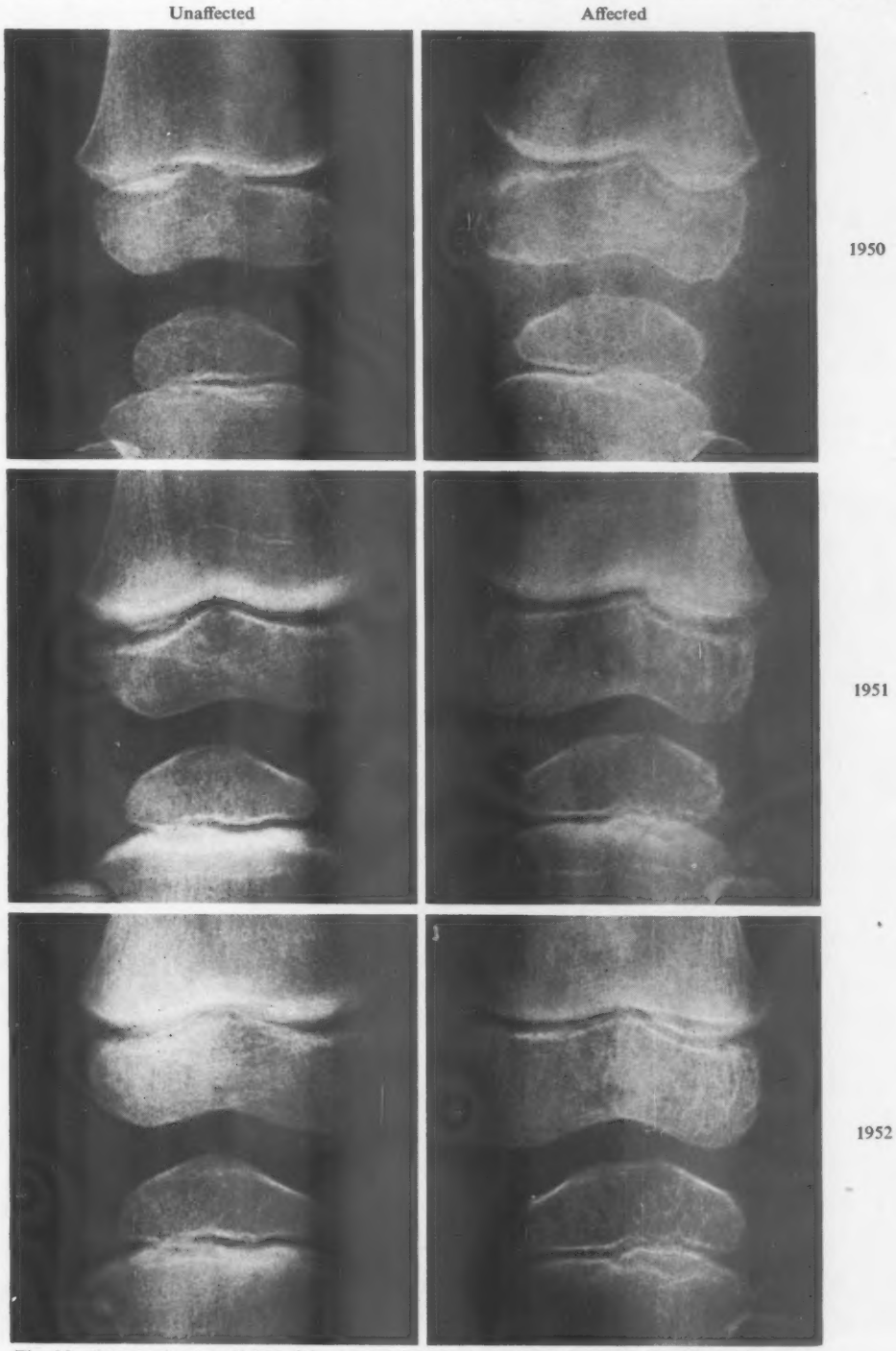


Fig. 14.—Increase in size of the epiphyses over 2 years, to a greater extent in the affected knee than the unaffected, showing dense metaphyseal line more marked on the normal side.

There were eight cases with unilateral involvement of the knee where assessment of growth was possible by measurement between Harris's lines (in other cases, the lines were not sufficiently distinct to allow certainty of identification). Measured by this means, growth and length of metaphyseal bone was often not affected by local disease (four cases), although there might be thickening due to periosteal accretion: at least one of these had been immobilized. In three instances there was overgrowth on the affected side; in the most severe case there was an increase of 1·9 and 0·5 cm. respectively between the epiphyseal lines of the femur and the tibia over and above the growth on the normal side. In two instances where this was found, it corresponded to a period of immobilization in plaster, and in the third it followed a period of prolonged rest in bed. Unilateral lengthening has been recorded from the time of Paget (1853) as a result of inflammation, and Dennison (1952) has noted it in a haemophiliac haemarthrosis, in tuberculosis of the hip, and in twenty out of eighty cases of osteomyelitis, affecting both of paired bones even if one only were infected. In only one case were the lesions of arrested growth produced by general somatic disturbance closer together on the affected than on the contralateral unaffected bone. The child was at home during this period and not immobilized. As seen in Fig. 15, these bony bands due to arrested metaphyseal growth may contain islets of unaltered cartilage.

(*c*) *Subperiosteal Accretion.*—Abnormal subperiosteal bone accretion occurs at all ages early in the

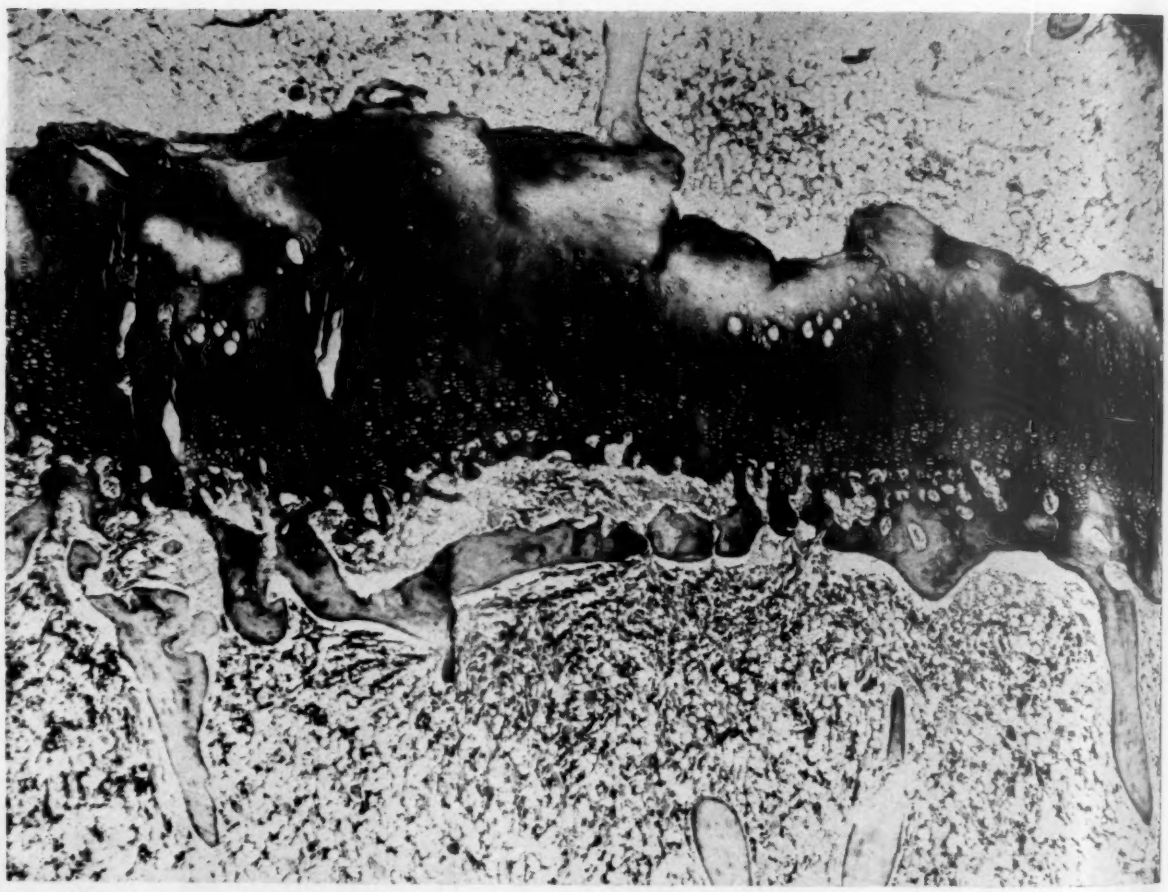


Fig. 15.—Photomicrograph (Leishman × 25) of epiphyseal line in a femur in a girl aged 13, showing line of arrested growth with cartilaginous inclusions.

course of the disease, tending to reabsorb in spite of continued activity of the disease (Fig. 16).

In other cases it blends with the bone and becomes therefore no longer recognizable except in series. This accretion was particularly pronounced in those under 5 years at onset, but it was not more frequent than in the older age group; it occurred in eighteen of the 31 patients under the age of 5, and in 27 of the 49 patients in whom the disease began after 5 years of age. In the phalanges this produced a curious picture somewhat resembling tuberculous dactylitis, with which it has been confused (Fig. 17). Reabsorption of this new bone seldom proceeds beyond normal, but sometimes subperiosteal absorption may (in the

Fig. 16.—Periosteal accretion in neighbourhood of fourth metacarpophalangeal joint with subsidence between the 18th and 27th month of the disease in a boy aged 11 at onset. Note premature epiphyseal fusion.

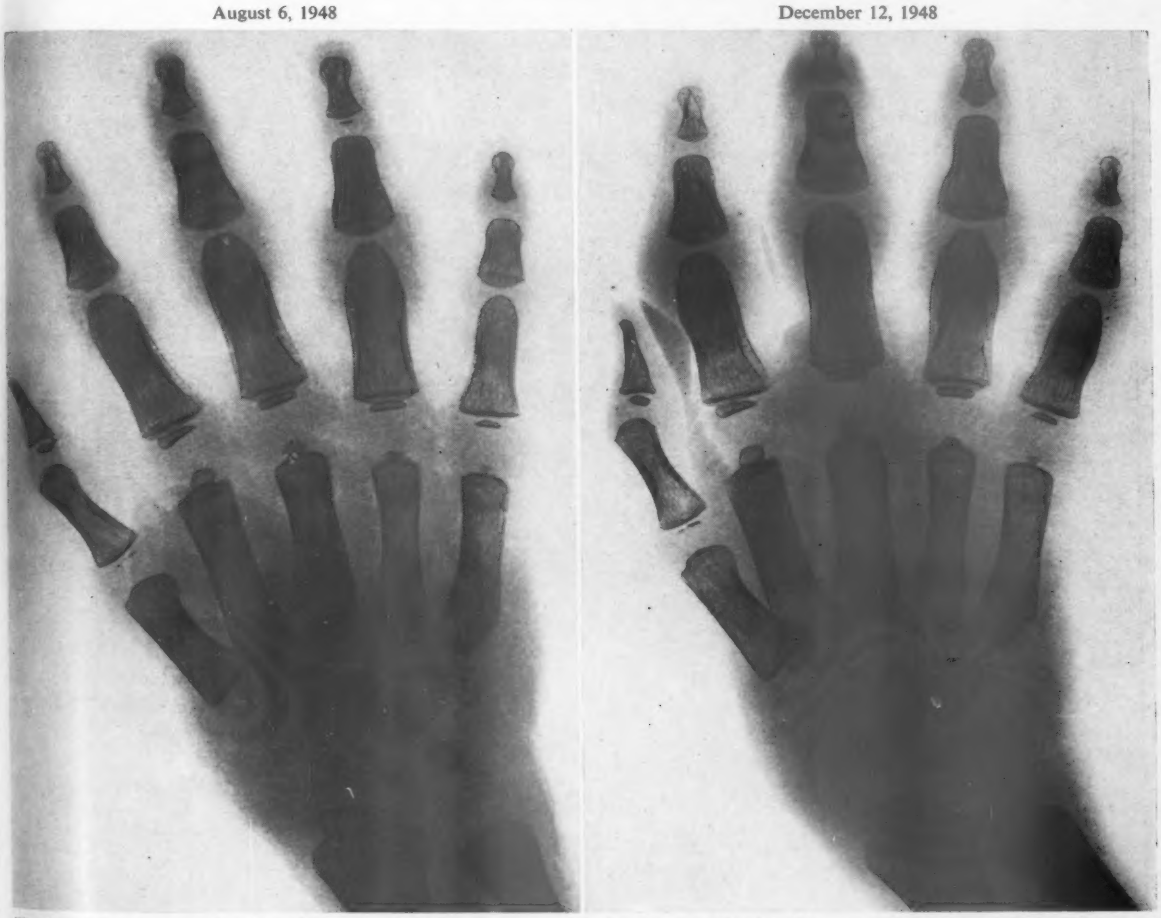


Fig. 17.—Advancement of periosteal accretion in the long bones of the hand, except the thumb, over a period of 4 months in a boy aged 2½ years who had had rheumatoid arthritis for 1¼ years.

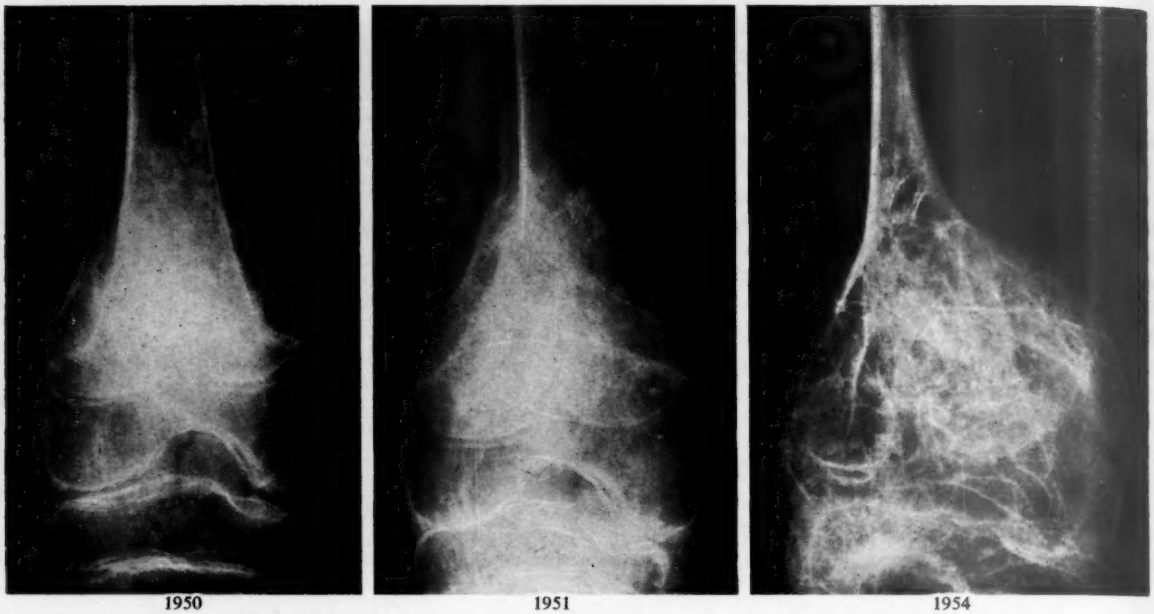


Fig. 18.—Tubular re-absorption of femur at 1, 2, and 5 years after fracture in a boy aged 10 in whom rheumatoid arthritis had begun one year previously.

absence of function and precipitated by fracture) lead to a marked thinning of the bone (Fig. 18). A brief account of the periosteal changes, radiological and pathological, has already been presented (Bywaters, 1948) and is to be published in detail.

(*d*) *Other Radiological Changes.*—Not infrequently the bony ends forming the terminal interphalangeal joints showed an overgrowth, and this was also seen to a lesser extent in the proximal interphalangeal joints, clinically resembling somewhat the nodes developing in old age and known by the names of Heberden and Bouchard respectively (Fig. 19). In the stage before the fusion

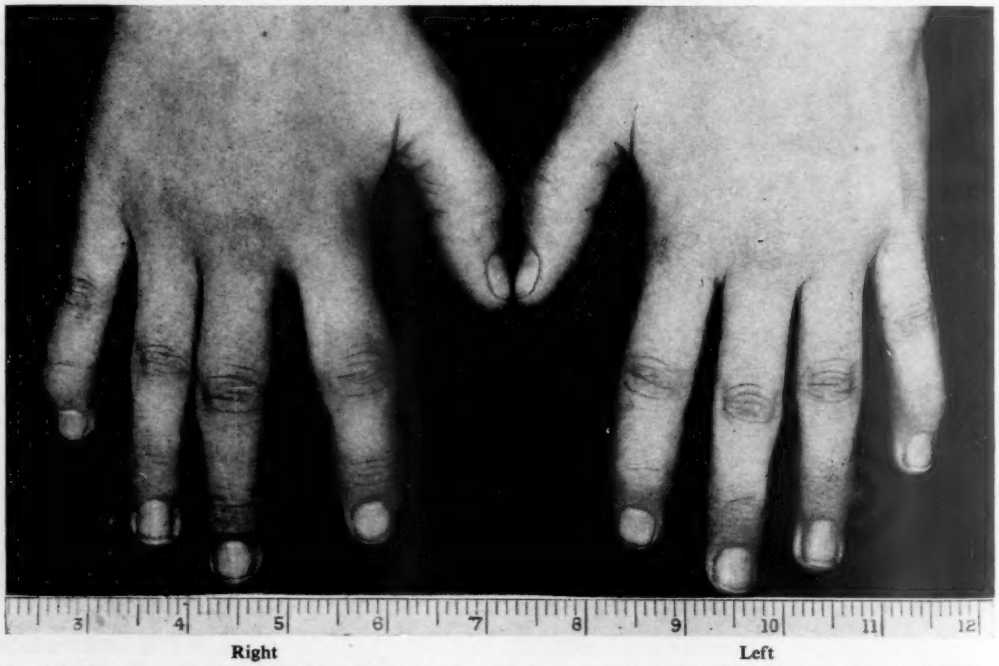


Fig. 19.—Bony overgrowth of the base of the terminal phalanges of the 2nd and 5th fingers without clinical or radiological involvement in a girl aged 14 with rheumatoid arthritis of one year's duration.

of the epiphyses, the terminal phalanges differed radiologically from those seen in degenerative joint disease, in that no bony outgrowth into the capsular ligament occurred (Fig. 20). This change occurred in seemingly unaffected joints and was due to enlargement and widening of the bony epiphysis; it was often accompanied by the enlargement of the non-growing middle phalangeal head, closely resembling that seen in old age (Fig. 21).

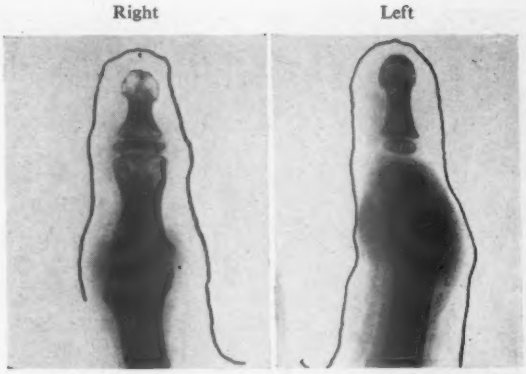


Fig. 20.—Overgrowth of terminal epiphysis clinically somewhat resembling Heberden's node in an affected (right) terminal index joint, compared with the contra-lateral (left) normal finger in a boy aged 12.

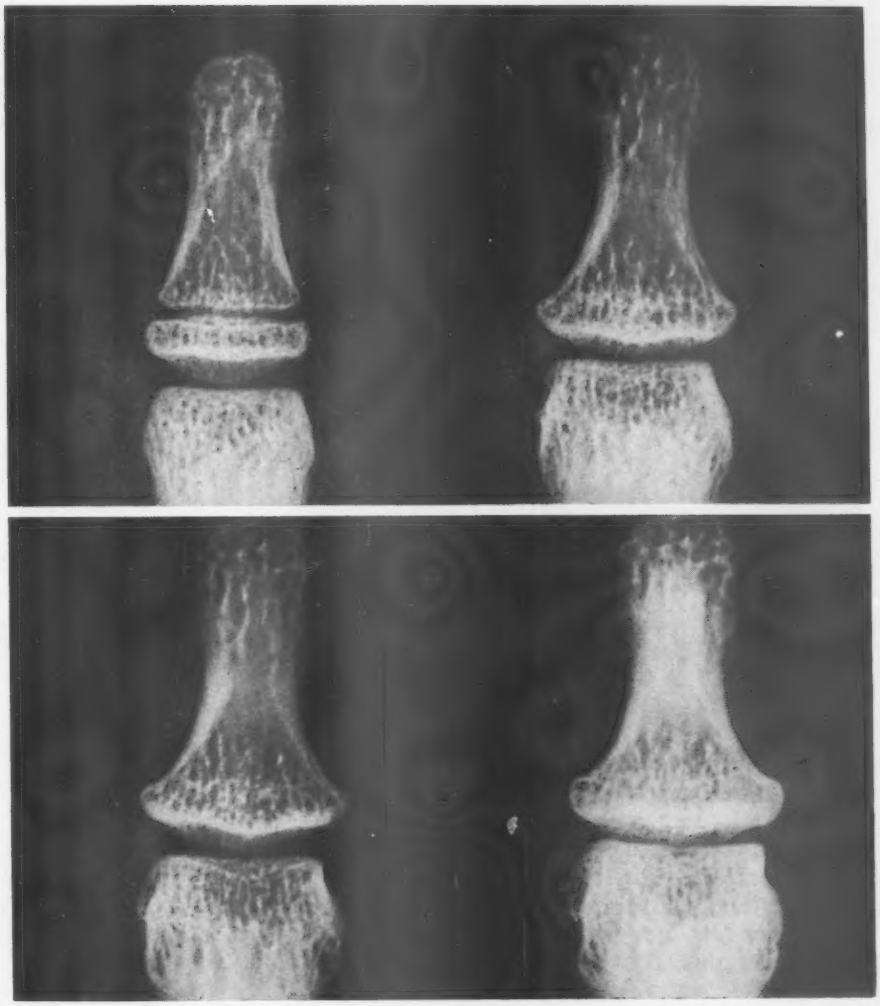
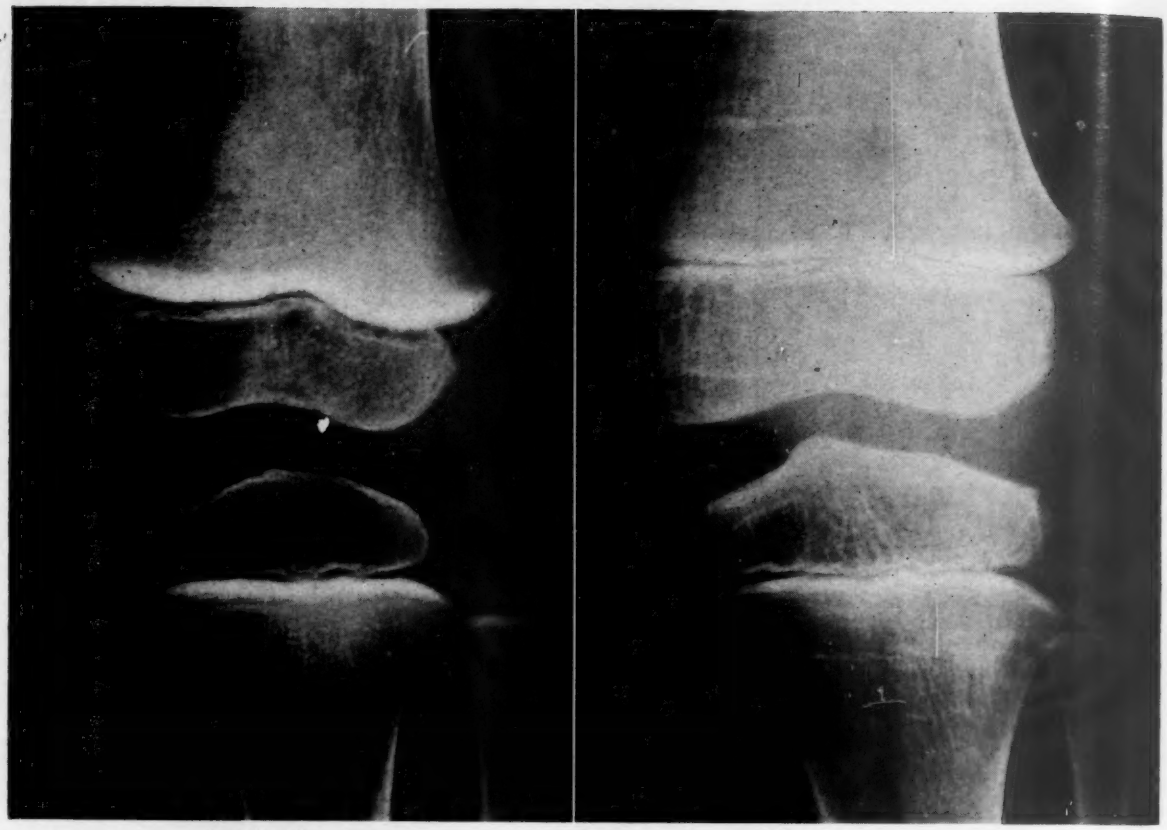


Fig. 21.—Overgrowth of epiphyses of uninvolved termina inter-phalangeal joint, developing over a period of 6 years in a girl aged 13 at onset. Note close similarity of phalangeal head to that of degenerative joint disease.



4 months after onset

After 2 years on cortisone

Fig. 22.—Dense metaphyseal band seen in a boy aged 3, 4 months after the onset of rheumatoid arthritis, and after 2 years on suppressive cortisone therapy. Note growth line in second *x* ray corresponding to previous band.

Another curious radiological phenomenon was the appearance of dense wide bands beneath the epiphyseal line (Fig. 22), somewhat resembling lead or bismuth lines (Caffey, 1937) or the phosphorus lines of the older literature (Phemister, 1918), and recalling the dense bands produced in rats on very large doses of cortisone (Follis, 1951). This was seen in three cases; it was present in one child on admission to hospital, in all bones, and disappeared one month later, never to reappear. It appeared in another child while under observation and lasted a considerable time; in a third child it was present on admission but disappeared rapidly when normal mobility was obtained under cortisone therapy. Investigations for lead in this case were negative. No history of excessive vitamin D dosage, or of lead, bismuth, or other metal intoxication was obtained in any of the cases and it seems possible that this is more akin to the dense bone which is seen in cases of myxoedema who are given thyroid (Hofmeister, 1897; Goetzky and White, 1914).

(4) Unilateral Wrist Involvement.—Although many patients have involvement of one wrist initially, this asymmetry is usually short-lived, and most cases ultimately become symmetrically involved. In cases with a considerable interval before the second wrist involvement, an opportunity is afforded for comparison with an unaffected wrist, although it must be remembered that growth on this seemingly normal side may be influenced by general changes due to the disease.

Fig. 23.—Case 3 from Table IV. Boy aged 9, with left carpal involvement, showing retardation of epiphyseal development on both sides. This retardation is much less marked on the affected side, which remains about 1 year behind the real age, while the unaffected side is 2 years behind the real age.

In the present series there were five children in whom only one wrist was involved for any considerable time; the period of involvement varied between 1 and 6 years. The unaffected side was chronologically equivalent to the actual age or was retarded by about 1 year. In all cases the carpal epiphysis on the affected side developed and remained in advance of the non-affected side by about 1 year (Fig. 23; Table IV, overleaf).

TABLE IV

CARPAL BONE AGE IN CASES WITH UNILATERAL INVOLVEMENT, COMPARED WITH ACTUAL AGE

Case No.	Duration of Carpal Involvement		Actual Age		Bone Age	
	Years	Months	Years	Months	Uninvolved	Involved
1	1	6	6	9	7	8
	2	8	7	11	8–9	9–10
	4	8	9	11	10	11
	5	6	10	9	11	Fusion of Carpus
2	2	0	7	0	6	7
	3	0	8	0	7	8
	4	0	9	0	9	10
3	1	6	9	6	6	7
	2	3	10	3	7	9
	3	2	11	2	9	10–11
	5	0	13	0	11	12½
4	0	1	14	0	13	13
	0	7	14	6	13	14
	0	10	14	9	13	15
	1	1	15	0	14	16
	2	1	16	0	14	17
5	3	0	15	0	15	16

In two cases all the epiphyses of the terminal interphalangeal joints (which were uninvolved) were markedly advanced compared with the unaffected side and were also in advance of the age of the child. In one of these two cases the sesamoid of the thumb also showed this phenomenon, appearing fifteen months in advance of the opposite side.

In this and other cases the bones of the affected arm were shorter than in the contra-lateral normal arm.

In two cases there was excessive hirsutism on the affected side.

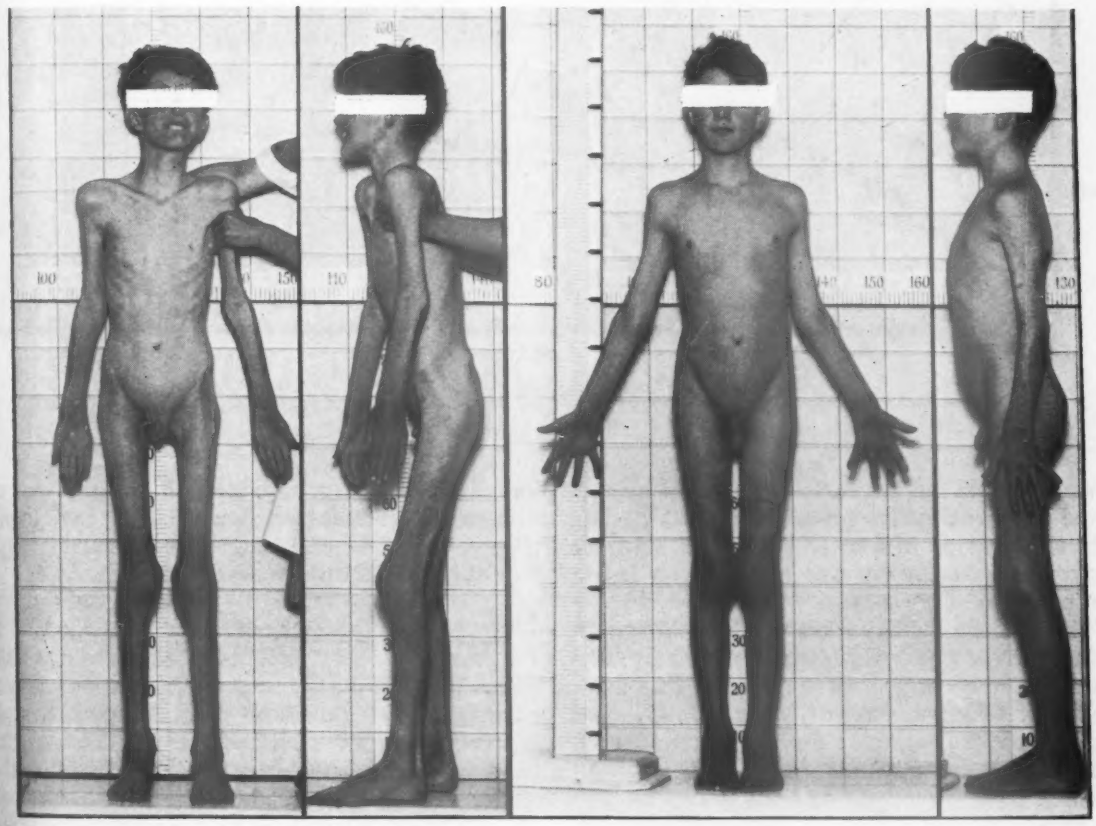
(5) Jaw Development.—One of the most arresting features of Still's disease is the maldevelopment of the lower jaw (Fig. 24). This was noticed to be present in 22 out of 152 cases of 16 years or under at onset, seven being male. A receding chin is sometimes seen in normal children but is seldom of marked degree. Thus, in only one of a series of 913 children with rheumatic fever seen between 1947 and 1955 was it marked enough to be noted, although a space is specifically allocated to this point both on the routine examination form in use here, and on the analytical index kept by the registrar dis-

Fig. 24.—Maldevelopment of jaw in Still's disease starting at the age of 3½ years; present age 11 years.

charging each case. This was not always associated with permanent involvement of the temporo-mandibular joints as evidenced by limitation of jaw separation, but it is difficult clearly to exclude previous involvement of this joint.

(6) **Sexual Maturity.**—In moderately severe cases there was some retardation in the development of secondary sexual characteristics. One child showed slight precocity in pubic hair formation, which was marked at 11 years; she had not received any hormone therapy.

(7) **Effect of Hormone Therapy on Weight and Height.**—All six children given methyl testosterone gained weight; this was particularly marked in those whose disease was becoming inactive (Fig. 25). Another patient not included in this series because



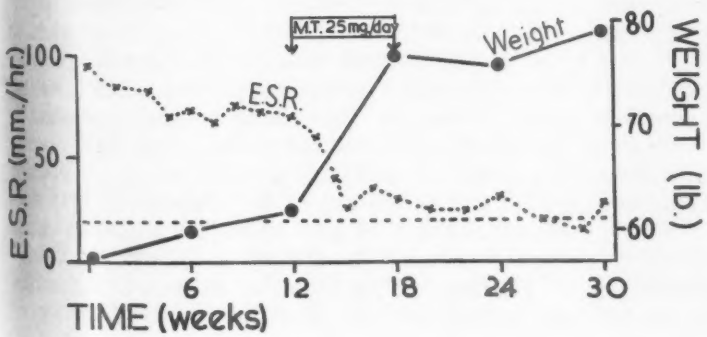


Fig. 25.—Weight gain during testosterone therapy in a boy aged 10 years with rheumatoid arthritis of one year's duration.

Fig. 26.—Weight gain during testosterone therapy in a girl.

she was 15 years old at onset and 16 when treated, showed an even more striking effect (Fig. 26). In the short period of 6 to 12 weeks that hormone therapy was given, there was no effect on height or on bone age of the carpus.

With cortisone therapy there was a rapid gain in weight, and despite mild dietary restriction, the majority of the early cases treated became more than 10 per cent. overweight. When hormone was stopped because the disease became inactive (seven cases), the weight fell to normal levels (Fig. 27, opposite).

In both early and late cases, long-term cortisone therapy was usually associated with a failure to grow in height despite good clinical control of the disease. In children under 5 years of age, dosage of 37·5 mg./day and over seemed to inhibit growth, while in the older age group this critical level appeared to be 50 mg./day (Fig. 28, overleaf). Once the dosage was reduced growth was resumed despite clinical activity; see Fig. 28D where cortisone was stopped because of complications.

In patients receiving cortisone, there was no apparent effect on bone development, although in the young, some prematurity, which was present initially, persisted despite control of activity of the disease. Two cases have shown definite radiological progression of the disease (Fig. 29, overleaf) despite the fairly satisfactory clinical control.

Discussion

Although Cornil (1864) described chronic arthritis occurring in children, Still (1897), in his classical description of the disease, was the first to note the general arrest of development. Following this, there were numerous single case reports, such as that of Hoppe-Seyler (1903), who described a 23-year-old woman with marked shortening of the limbs, assumed to be due to her arthritis which had begun at the age of 7 years. Other case reports include that of Dock (1912), who described a man aged 24 who had reduced limb growth due to arthritis dating from the age of 11. Eliakim (1922) described a similar shortening of the limbs, particularly in the forearms, in a man of 58 years in whom the disease had begun at the age of 9. Algyogyi (1909) described dwarfism in a 20-year-old woman in whom the disease had begun at 6 years. Kuhns and Swaim (1932) reviewed the literature on growth defects in chronic arthritis and described twelve of their own

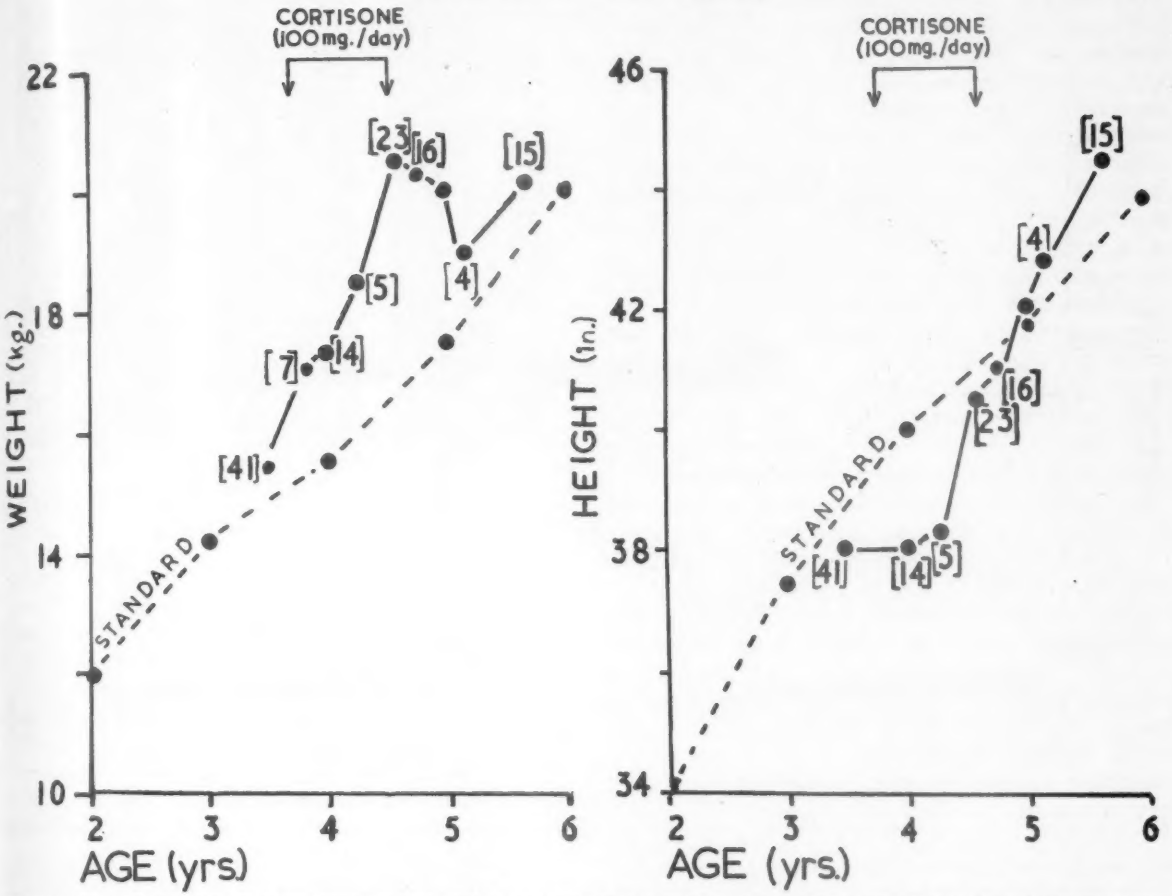


Fig. 27.—Suppression of disease by cortisone was accompanied by a rapid gain in weight. Restoration of growth as height was not seen initially on cortisone and occurred only when the disease activity subsided.

cases. They felt that these disturbances of growth could be divided into three types: a generalized retardation of body growth, a persistence of the infantile appearance and proportions of the extremities, and asymmetry of growth. This suggested that the type of disturbance depends on the severity and location of the disease. As more cases were reported, these defects were seen to be not uncommon; thus four of the 28 cases described by Lockie and Norcross (1948) had interference with bone growth, and 22 of the fifty cases described by Coss and Boots (1946) showed a disturbance of the skeletal pattern, the two most frequent abnormalities encountered being brachygnathia and brachydactylia. Both accounts agreed that these deformities were more likely when the disease had begun early in life. Middlemiss (1951), in a series of over forty cases, notes that the changes are more frequent later in the disease.

In our cases, the failure of normal growth in height and weight was closely associated with the activity of the disease, occurring early and tending to correct itself as the disease became inactive, so that only in long-standing cases was there severe general stunting in the absence of premature fusion of epiphyses. The commonest radiological evidence of growth disturbance were growth lines in the metaphyses, which might occur equally in the radius for instance, in those with and without wrist involvement. These lines are due to temporary arrest of cartilaginous growth and are entirely non-specific, having originally been described in Great Britain by Harris (1933) in various acute illnesses, particularly broncho-pneumonia. Hewitt, Westropp, and Acheson (1955) recently emphasized the frequency with which these occur in healthy children as the result of minor ailments. Most of the bizarre growth anomalies in our series developed as a result of local disease and were due directly to premature fusion of the epiphyses. Premature epiphyseal fusion occurred more commonly in the older age group, and affected particularly the metacarpal

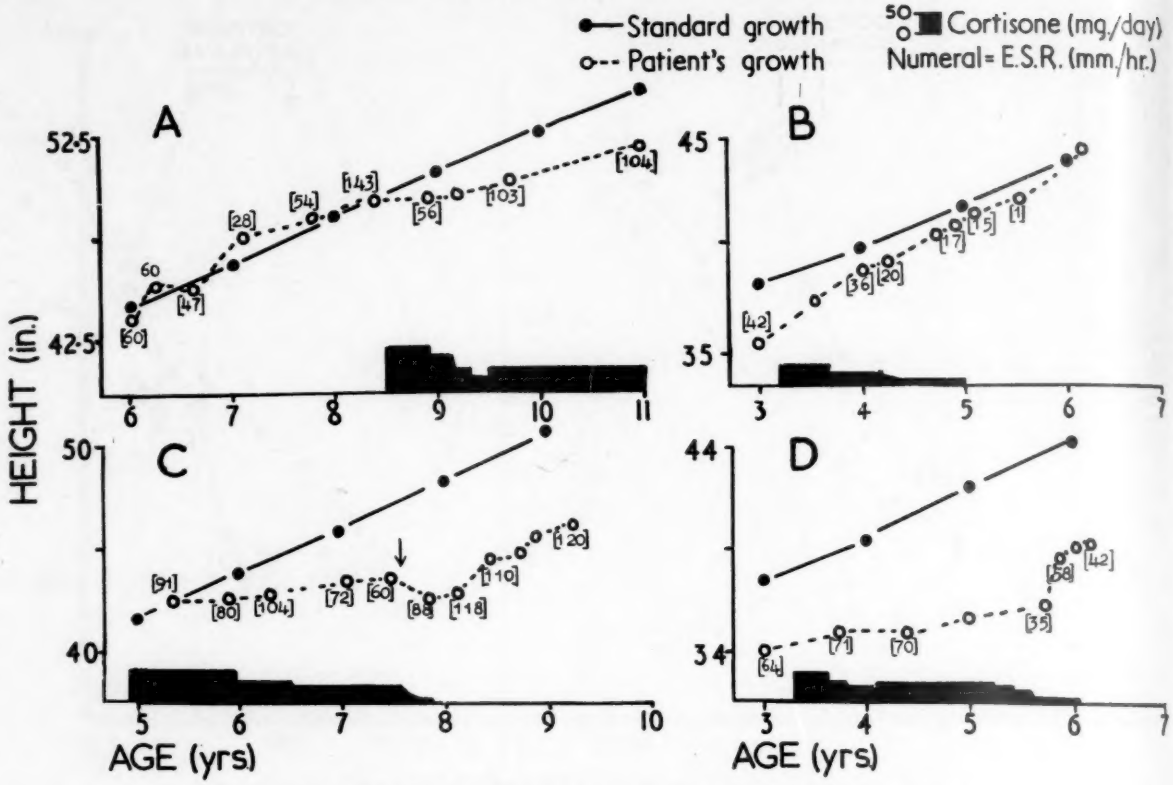


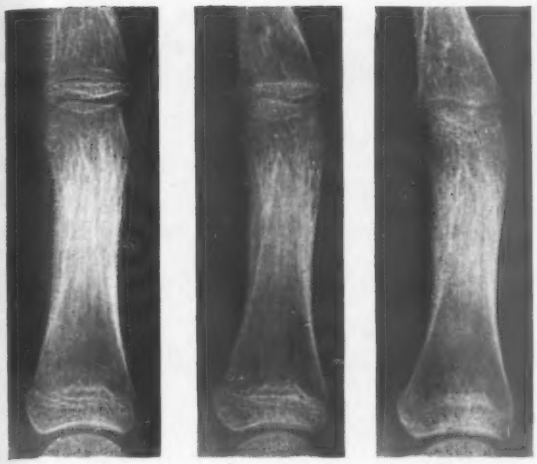
Fig. 28.—Effect of prolonged cortisone therapy on the rate of growth as height in children.

(A) Male, onset at 2 yrs with severe relapse at 8 yrs 4 mths when cortisone therapy was begun.
(B) Female, onset at 2 yrs 9 mths, mild activity well controlled by small doses of cortisone.
(C) Female, onset at 15 mths, persistent activity for 11 mths before cortisone therapy was begun. ↓ = crush fracture of vertebra.
(D) Female, onset at 1 yr, persistent marked activity with fever until cortisone therapy was begun.

bones and phalanges. Our results are in general agreement with those of Coss and Boots (1946) in that the most severe deformities are seen when the disease commences early in life and continues for a long period, but we have found that the most frequent deformity, brachydactylia, is more common in the older age group and may occur fairly quickly. Short of premature fusion, there was no obvious difference between the cases which showed advancement and those who showed retardation of epiphyseal development in the affected limb. However, in all five cases with unilateral wrist involvement, the unaffected side was retarded in comparison with the affected side and with chronological age as described by Françon, Forestier, and Robert (1937). Metaphyseal growth was sometimes increased on the affected side in comparison with the unaffected side in immobilized cases.

The mechanism of these disturbances of growth is unknown. In the healthy, well-fed child, growth proceeds until shortly after puberty. The rate of growth would appear to be under the control of the pituitary growth hormone, but its cessation is largely determined by the time of epiphyseal union. The cause of growth cessation is unknown, and may be due either to a factor which inhibits the growth hormone, or to one which works on the end organs.

In juvenile rheumatoid arthritis, marked defects of general growth are seen only in severe cases and it could be that the disease causes inhibition of the pituitary growth factor. In favour of this is the delayed development of secondary sex characteristics, which is common in these cases, but there are no other signs of pituitary failure, and in six of our patients between the ages of 7 and 14 years, who showed general stunting, the excretion of 17-ketosteroids was within the range of normal values for children given by Talbot, Butler, Berman, Rodriguez, and MacLachlan (1943). Even if the general growth failure were due to pituitary failure, it could not account for the local variation in epiphyseal development. This fact is particularly clear in patients with unilateral wrist involvement. Here in all cases the affected wrist was in advance of the



5 months 10 months 15 months

Fig. 29.—Progression of erosion in proximal interphalangeal joint at 5, 10, and 15 months from onset, cortisone being given in suppressive dosage from the fifth month.

unaffected one, which might or might not be retarded. Thus one would have to postulate a generalized inhibiting factor due to the disease itself and a local accelerating factor due to local joint involvement. That a local factor is at work is suggested by the hirsutism seen on the affected limb. It might be postulated that the increased vascularity resulting from active joint involvement which produces the local rise in temperature over an involved joint and affects the skin and soft tissues, could also affect the bone and thus cause bony overgrowth; this is well recognized as a local consequence of haemangiomata, cirsoid limb aneurysms, and arterio-venous fistulae (Ward and Horton, 1940).

The cause of premature fusion of epiphyses is also unknown. In tuberculosis of the hip, premature closure of the epiphyseal cartilage of the lower end of the femur where there is marked decalcification has been described (Gill, 1944; Ross, 1948). It is also suggested that immobility causes degeneration of the epiphyseal cartilage with subsequent bridging (Sissons, 1952). Osteoporosis occurs early in the course of rheumatoid arthritis and, when joints are severely affected, that limb is frequently kept at rest. However, fusion can also occur without either of the above factors being present.

Although patients put on weight on cortisone therapy, normal growth as height was not resumed until the cortisone was reduced below a certain critical level either because the disease became inactive or because of toxic complications or other reasons.

Bunim, Ziff, and McEwen (1955) found that prolonged hormone therapy in Still's disease allowed growth as height to return to normal levels in five out of eight cases, in only one of whom had they been able to discontinue cortisone therapy. As he does not state his dosage, however, this experience does not necessarily conflict with ours. This slowing of children's growth has also been shown to occur with cortisone in several endocrine diseases of childhood and in allergy (Blodgett, Burgin, Iezzoni, Gribetz, and Talbot, 1956). Using the Greulich-Pyle standard, they also noted that the rate of skeletal maturation in eleven children with congenital hypercortical activity was decreased from their previously increased levels. Our findings of decreased growth as height with little effect on skeletal maturation during cortisone therapy rather resemble those described by Hewitt and others (1955) in intercurrent illness.

The courses of testosterone we gave were too short to influence bony development. In all instances there was weight gain and this was particularly marked when the disease was becoming less active.

We conclude that in Still's disease there is a general retardation of growth affecting both height and weight, as in other chronic diseases of childhood either inflammatory or metabolic.

Skeletal maturation is, however, not beyond a range of one year from real age, unless local disease is present. Local disease may lead to increased or decreased metaphyseal growth rates, to premature epiphyseal development, and sometimes to premature fusion.

Steroid therapy above a certain dosage inhibits growth in height but not skeletal maturation.

Summary

Changes in height, weight, and bone growth have been followed over a period of years in 119 cases of Still's disease (defined for this purpose as rheumatoid arthritis starting before the age of 14 years). Abnormality was defined by comparison with published normal standards and with a small series of rheumatic fever patients.

Height was temporarily decreased more than 10 per cent. below normal in about half the children measured, but in many of the younger children, when the disease became quiescent, growth was rapidly resumed and returned to the standard level. Weight was lost at onset, remained low during disease activity, and resumed normal levels with quiescence. Only with fever and prolonged disease activity were marked residual defects in height and weight observed.

In children without hand involvement, carpal maturity was within one-year limits of normality,

but in half the cases where the carpus or wrist were involved, carpal development was advanced.

Abnormalities of bone development occurred primarily in the neighbourhood of the affected joints. These included premature epiphyseal fusion, particularly in the older group, leading to shortened bones, increase in epiphyseal size and in longitudinal growth of the metaphysis, temporary decrease or arrest of bone growth manifest as growth lines and double-contoured epiphyses, and minor changes such as periostitis, dense metaphyseal bands, and subchondral bony outgrowths of the epiphyses.

These changes can be ascribed to a general non-specific retardation of growth, such as is seen in any long-standing generalized disease of childhood, and to a local effect in the neighbourhood of involved joints, possibly due to increased blood flow, which produces a temporary acceleration of development and sometimes of growth, but more usually a decreased growth rate or premature epiphyseal fusion.

Male sex hormone over short periods caused in some children a rapid gain in weight which was maintained; cortisone therapy over prolonged periods produced the usual temporary obesity and a slowing of growth in height at all but minimal levels of dosage. There was little apparent effect on skeletal maturation.

REFERENCES

Adams, F. H., and Forsyth, W. B. (1951). *J. Pediat.*, **39**, 330.
Algyogyi, H. (1909). *Mitt. Ges. inn. Med. Wien*, **8**, 103.
Barkin, R. E. (1952). *Bull. rheum. Dis.*, **3** (no. 1), p. 19.
Beal, C. K. (1948). *J. Pediat.*, **32**, 170.
Blodgett, F. M., Burgin, L., Iezzoni, D., Gribetz, D., and Talbot, N. B. (1956). *New Engl. J. Med.*, **254**, 636.
Bogan, I. K. (1940). *Amer. J. Dis. Child.*, **59**, 805.
Bunim, J. J., Ziff, M., and McEwen, C. (1955). *Amer. J. Med.*, **18**, 27.
Bywaters, E. G. L. (1948). *Annals of the Rheumatic Diseases*, **7**, 24.
Campbell, M., and Reynolds, G. (1949). *Arch. Dis. Child.*, **24**, 294.
Caffey, J. (1937). *Amer. J. Dis. Child.*, **53**, 56.
Cohen, M. B., and Abram, L. E. (1948). *J. Allergy*, **19**, 165.
——, Weller, R. R., and Cohen, S. (1940). *Amer. J. Dis. Child.*, **60**, 1058.
Cornil, V. (1864). *Mém. Soc. Biol.* (*Paris*), Ser. 4, **1**, 3.
Coss, J. A., and Boots, R. H. (1946). *J. Pediat.*, **29**, 143.
Daley, A. (1950). London County Council, No. 3692. "Report on the Heights and Weights of School Pupils in the County of London in 1949."
Dennison, W. M. (1952). *Arch. Dis. Child.*, **27**, 54.
Dock, G. (1912). *Amer. J. med. Sci.*, **144**, 469.
Edström, G. (1947). *Acta paediat.*, **34**, 334.
Eliakim, S. (1922). *Z. Kinderheilk.*, **33**, 55.
Ellis, A., and Evans, H. (1933). *Quart. J. Med.*, **2**, 231.
Findlay, L., and Graham, S. (1927). *Arch. Dis. Child.*, **2**, 71.
Follis, R. H., Jr. (1951). *Proc. Soc. exp. Biol.* (*N.Y.*), **76**, 722.
Françon, F., Forestier, J., and Robert, P. (1937). *J. Radiol. Electrol.*, **21**, 5.
Gaunt, R. T. (1949). *Lancet*, **1**, 1049.
Gill, G. G. (1944). *J. Bone Jt Surg.*, **26**, 272.
Goetzky, F., and White, F. (1914). *Z. Kinderheilk.*, **11**, 179.
Greulich, W. W., Crismon, C. S., and Turner, M. L. (1953). *J. Pediat.*, **43**, 121.
—— and Pyle, S. I. (1950). "Radiographic Atlas of Skeletal Development of the Hand and Wrist, based on the Brush Foundation Study of Human Growth and Development initiated by T. Wingate Todd." University Press, Stanford, California.
Halbertsma, T. (1933). *Amer. J. Dis. Child.*, **46**, 1356.
Harris, H. A. (1933). "Bone Growth in Health and Disease." Oxford University Press, London.
Harris, R. I. (1930). *J. Bone Jt Surg.*, **12**, 859.
Hernberg, C. A., and Heikel, P. E. (1951). *Acta paediat.*, **40**, 486.
Hewitt, D., Westropp, C. K., and Acheson, R. M. (1955). *Brit. J. prev. soc. Med.*, **9**, 179.
Hofmeister, F. (1897). *Fortschr. Röntgenstr.*, **1**, 4.
Holt, L. E., Jr., and McIntosh, R. (1941). "Holt's Diseases of Infancy and Childhood", 11th ed. Appleton-Century, New York.
Hoppe-Seyler, G. (1903). *Dtsch. Arch. klin. Med.*, **75**, 320.
Kuhns, J. G., and Swaim, L. T. (1932). *Amer. J. Dis. Child.*, **43**, 1118.
Langston, W. (1935). *Sth. med. J.*, **28**, 316.
Lockie, L. M., Norcross, B. M. (1948). *Pediatrics*, **2**, 694.
Lund, G. W. (1952). *J. Pediat.*, **41**, 572.
Mainland, D. (1953). *Pediatrics*, **12**, 114.
Menzies, F. (1940). London County Council, No. 3464. "Report by the School Medical Officer on the Average Heights and Weights of Elementary School Children in the County of London in 1938."
Middlemiss, J. H. (1951). *Proc. roy. Soc. Med.*, **44**, 805.
Paget, J. (1853). "Lectures on Surgical Pathology", vol. 1. Longmans, London.
Phemister, D. B. (1918). *J. Amer. med. Ass.*, **70**, 1737.
Ross, D. (1948). *J. Bone Jt Surg.*, **30A**, 103.
Sissons, H. A. (1952). *Ibid.*, **34B**, 275.
Still, G. F. (1897). *Med.-chir. Trans.*, **80**, 47 (reprinted in *Arch. Dis. Child.*, 1941, **16**, 156).
Talbot, N. B., Butler, A. M., Berman, R. A., Rodriguez, P. M., and MacLachlan, E. A. (1943). *Amer. J. Dis. Child.*, **65**, 364.
Sury, B. (1952). "Rheumatoid Arthritis in Children: a Clinical Study." Munksgaard, Copenhagen.
Ward, C. E., and Horton, B. T. (1940). *J. Pediat.*, **16**, 746.
Welsh, J. B. (1951). *Ibid.*, **38**, 571.

La croissance dans la maladie de Still

RÉSUMÉ

Les modifications de taille, de poids et de croissance des os ont été suives durant plusieurs années, dans 119 cas de maladie de Still (définie en l'occurence comme arthrite rhumatismale survenant avant l'âge de 14 ans). Les anomalies ont été définies par comparaison avec des standards normaux publiés et avec un petit groupe de malades atteints de rhumatisme articulaire aigu.

La taille était temporairement diminuée de plus de 10% au-dessous de la normale chez environ la moitié des enfants mesurés, mais chez beaucoup d'enfants plus jeunes la croissance reprenait et revenait rapidement au niveau normal dès l'arrêt de l'activité morbide. Le poids, perdu au début, demeurait bas à la période évolutive et remontait au niveau normal à la période de rémission. Seulement dans les cas de fièvre et d'activité morbide prolongée pouvait on observer des défauts résiduels marqués de taille et de poids.

Chez les enfants dont les mains n'étaient pas atteintes, la maturité du carpe se trouvait à une année près de la normale, mais dans le moitié des cas où le carpe ou le poignet se trouvait atteint, le développement carpien était avancé.

Des anomalies de développement osseux se produisaient d'abord au voisinage des articulations atteintes. Elles comprenaient: la fusion épiphysaire prématurée, en particulier chez les enfants plus âgés, ce qui conduisait à un racourcissement osseux; accroissement de l'épiphyse et allongement de la métaphyse; une diminution ou l'arrêt temporaire de la croissance osseuse, manifestes sous formes de lignes de croissance et d'épiphyses à double contour, et des altérations mineures, telles que périostite, bandes métaphysaires denses et excroissances osseuses souschondrales des épiphyses.

Ces altérations peuvent être imputées à un retard généralisé, non-spécifique, de la croissance, tel qu'on peut en observer dans n'importe quel cas de maladie généralisée et de longue durée de l'enfance, et à un effet local dans le voisinage des articulations atteintes,

probablement dû à une plus forte irrigation sanguine, produisant une accélération temporaire du développement et parfois de la croissance, mais plus souvent un rhythme de croissance diminuée ou une fusion épiphysaire prématurée.

L'hormone sexuelle mâle administrée durant de courtes périodes produisait chez quelques enfants un gain rapide de poids qui était maintenu; la thérapie stéroide sur des périodes prolongées produisait l'obésité temporaire habituelle et un ralentissement de l'augmentation de taille à tous les dosages, sauf en quantité minime. Il y avait peu d'effet apparent sur la maturation du système ostéo-musculaire.

El crecimiento en la enfermedad de Still

SUMARIO

Las modificaciones de estatura, peso y crecimiento óseo fueron seguidas duranto algunos años en 119 cases de énfermedad de Still (definida aquí como artritis reumatoide empezando antes de la edad de 14 años). Las anomalías fueron definidas en comparación con normas publicadas y con un pequeño grupo de enfermos con reumatismo poliarticular agudo.

La estatura fué temporariamente disminuida de más de 10% de la norma en cerca de la mitad de los niños medidos, pero en muchos niños jóvenes en el período de quietud de la enfermedad hubo un reanudo rápido del crecimiento hasta alcanzar la norma. El peso perdido al principio de la enfermedad quedaba bajo durante la actividad mórbida pero subía al nivel normal durante el período de quietud. Tan sólo en casos de fiebre y de actividad mórbida prolongada pudiéronse observar defectos residuales marcados de estatura y de peso.

En los niños cuyas manos no fueron implicadas, el estado madurativo del carpo se alejaba de un año de la norma, pero en la mitad de los cases de implicación del carpo o de la muñeca el desarrollo del carpo estaba adelantado.

Anomalías de desarrollo óseo producíanse primeramente cerca de las articulaciones implicadas. Estas comprendían: fusión epifisaria prematura, en particular en niños mayores, lo que producía huesos más cortos; agrandecimiento de la epífisis y crecimiento longitudinal de la metáfisis; disminución o interrupción temporaria del crecimiento óseo, manifestándose en líneas de crecimiento y en epífisis con doble contorno; y alteraciones menores, como periostitis, fajas metáfisarias densas y excrecencias óseas subcondrales de las epífisis.

Estas alteraciones pueden atribuirse a un atraso generalizado, no específico del crecimiento, de tipo que se puede notar en cualquier caso de enfermedad generalizada y persistente de la infancia, y a un efecto local alrededor de las articulaciones implicadas, probablemente a conseciencia del riego sanguíneo aumentado con acceleración temporaria del desarrollo y a veces del crecimiento, pero más a menudo con ritmo de crecimiento disminuido o con fusión epifisaria prematura.

La hormona sexual masculina administrada durante períodos cortos producía en algunos niños un aumento de peso que se mantenía. La terapia esteroide prolongada conducía a la obesidad temporaria habitual y al retraso de crecimiento de la estatura con todas las dosis, exceptuando las dosis mínimas. No hubo efecto aparente sobre la maduración del sistema óseo-muscular.

Ann. rheum. Dis. (1956), **15**, 320.

STUDIES IN OSTEO-ARTHRITIS USING INTRA-ARTICULAR TEMPERATURE RESPONSE TO INJECTION OF HYDROCORTISONE ACETATE AND PREDNISONE

BY

JOSEPH L. HOLLANDER AND ROBERT MOORE

From the Arthritis Section, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pa

(RECEIVED FOR PUBLICATION SEPTEMBER 27, 1956)

The use of intra-articular hydrocortisone acetate in the treatment of osteo-arthritis has been shown to produce a temporary improvement of symptoms in many cases (Hollander, Stoner, Brown, and De Moor, 1951), although enthusiasm for this method has been tempered by warnings of the possibility of increasing the damage in joints subjected to excessive use in the periods of freedom from symptoms (Young, Ward, and Henderson, 1954). The results of treatment of the knee have been more encouraging than those of treatment of other joints, presumably because of the ease with which injection of the knee joint can be accomplished.

The present study has been undertaken in a series of patients with osteo-arthritis, to determine what changes occur in the intra-articular temperature, before and after the injection of hydrocortisone acetate or prednisone into the knee joint. An endeavour was also made to correlate these temperature changes with the relief of symptoms in the affected joint.

Materials and Method

26 cases of osteo-arthritis were studied. All complained of pain, stiffness, swelling, and limitation of movement of varying degree in one or both knees, effusions were present in the joint in twelve cases, and the erythrocyte sedimentation rate was in no case above 36 mm./hr (normal 20 mm./hr—Wintrobe method). The cases were divided into five groups, the particulars of which are contained in Table I (opposite).

Group 1.—A control group of five patients. Three were females suffering from generalized osteo-arthritis (Kellgren and Moore, 1952) and showed the characteristic Heberden nodes, and first carpometacarpal arthritis in addition to arthritis of the knees and other joints. In the other two patients, who were males, the symptoms were localized to the knees. One had been a carpenter for many years his occupation necessitating a great deal of kneeling, while the other had marked bowing of the tibiae following rickets in childhood and this appeared to have thrown a strain on the knees. Whether these constitute cases of osteo-arthritis due to repeated minor trauma remains uncertain, but the knees alone were involved.

All five cases were investigated without injection of a therapeutic substance, and in two cases both knees were examined, making a total of seven joints in the control group. However, two knee joints were injected with the inert aqueous vehicle used for the suspension of hydrocortisone acetate.

Group 2.—Sixteen patients suffering from generalized osteo-arthritis. Ten of these were submitted to the whole investigation. One of the female controls also appears in this group. Intra-articular hydrocortisone acetate was administered.

Group 3.—The two male controls. Intra-articular hydrocortisone acetate was administered.

Group 4.—Five patients suffering from osteo-arthritis of the knees which was apparently secondary to the strain of weight-bearing from obesity. Intra-articular hydrocortisone acetate was administered.

Group 5.—Three patients suffering from generalized osteo-arthritis. Two of these had previously been used in the Group 2. This series received prednisone intra-articularly.

The knee joint was chosen for intra-articular studies because it is relatively easy of access. All the subjects reclined on a couch, with the legs and feet uncovered from just above the knee, for one hour before the tests, in a room maintained at 25–26° C. After the skin on the medial aspect of the patella had been sterilized, a 19-gauge needle was inserted into the joint without preliminary local anaesthesia, producing only temporary discomfort during the introduction. Fluid when present was aspirated. A filamentous copper-constantan thermocouple was passed through the needle into the joint, and the electromotive force developed in the

TABLE I

PARTICULARS OF PATIENTS

Group	Diagnosis	Case No.	Sex	Knee	Age (yrs)	Height (in.)	Weight (lb.)	Erythrocyte Sedimentation Rate (mm./hr Wintrobe)
1 Controls	Generalized Osteo-Arthritis	1	F	R, L	77	66	144	28
		2	F	R	64	65	141	35
		3	F	R	62	61	154	26
	Traumatic Arthritis	4	M	L	61	65	167	15
		5	M	R	64	64	170	29
2 Hydrocortisone Acetate	Generalized Osteo-Arthritis	6	F	L	67	64½	158	20
		7	F	R	76	60	148	24
		8	F	R	56	62	144	19
		9	F	L	57	63	148	22
		10	F	R	62	66	170	14
		11	F	L	51	62½	163	20
		12	F	L	67	60	133	24
		13	F	R	77	64	165	18
		14	F	R	62	60	140	26
		15	F	L	69	59	111	30
		16	F	R	65	65	134	26
		17	F	R	62	66½	170	14
		18	F	L	51	62	160	22
		19	F	R	59	58	126	29
		20	F	R	65	63	172	36
3 Hydrocortisone Acetate	Traumatic Arthritis	4	M	R	61	65	167	15
		5	M	R	64	64	170	29
4 Hydrocortisone Acetate	Obesity with Osteo-Arthritis	21	F	L	63	61	167	24
		22	F	L	67	64	184	36
		23	F	L	56	60	180	35
		24	F	R	49	60	176	25
		25	F	R	54	61	184	20
5 Prednisone	Generalized Osteo-Arthritis	7	F	R	76	60	148	24
		14	F	R	62	60	140	26
		26	F	L	68	60	179	30

thermocouple was measured by a Brown Automatic-recording Potentiometer, the result being expressed in °C. and recorded directly on a moving chart. Readings from the intra-articular lead were recorded at intervals of one and a half minutes. When the temperature record had become stationary, usually in 45 minutes, the lead was disconnected from the patient and hydrocortisone acetate 37·5 mg. in 1·5 ml. solution, or prednisone 15 mg. in 1·5 ml. solution, was injected into the joint through the needle. The appearance of the synovial fluid was noted, its viscosity roughly tested by the drop technique (Hollander, 1953), and its mucin clot formation with dilute acetic acid examined. A cell count was done using undiluted fluid, and a smear made for differential counts. The studies were repeated at the end of 24 hours, and 48 hours, and then after 5 days. Only one injection of hydrocortisone acetate or prednisone was given in each study.

Results

Controls

The preliminary intra-articular temperature for the group fell within the range of 31·5 to 36° C. (Fig. 1; and Table II, overleaf). It rose in four knee joints in the first 24 hours, the maximum rise being

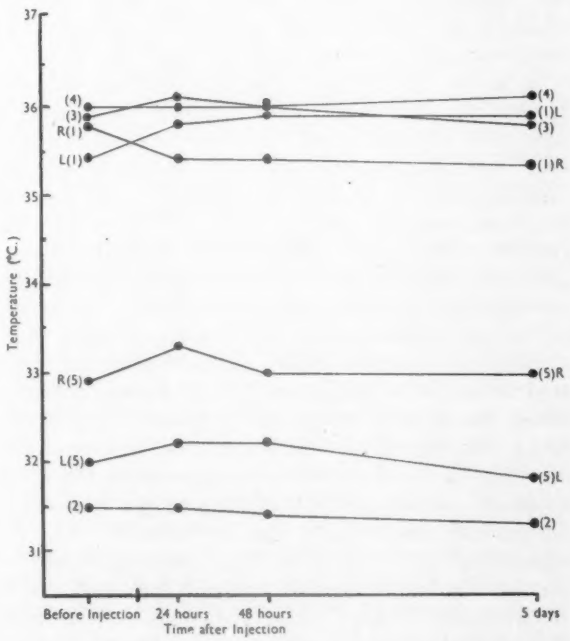


Fig. 1.—Intra-articular temperature changes in controls.

TABLE II

INTRA-ARTICULAR TEMPERATURE (°C.)

Group	Case No.	Knee	Before	After		
				24 hrs	48 hrs	5 days
1 Controls	1	R	35·8	35·4	35·4	35·3
		L	35·4	35·8	35·9	35·9
	2	R	31·5	31·5	31·4	31·3
	3	R	35·9	36·1	36·0	35·8
	4	L	36·0	36·0	36·0	36·1
	5	R	32·9	33·3	33·0	33·0
		L	32·0	32·2	32·2	31·8
2 Hydrocortisone Acetate	1	L	35·8	36·3	36·2	35·9
	6	L	34·3	34·8	33·4	32·2
	7	R	35·4	35·5	35·9	35·3
	8	R	35·0	35·6	34·6	34·6
	9	L	33·6	34·5	35·2	34·8
	10	R	34·4	35·9	36·4	36·1
	11	L	34·4	34·7	34·9	34·7
	12	L	35·8	36·3	36·3	35·8
	13	R	35·0	35·6	35·5	34·6
	14	R	35·4	36·2	35·6	35·1
3 Hydrocortisone Acetate	4	R	35·4	35·8	36·3	36·2
	5	R	33·2	34·2	34·2	33·8
4 Hydrocortisone Acetate	21	L	35·9	35·8	35·3	35·4
	22	L	36·3	36·4	36·4	36·0
	23	L	35·8	35·8	35·2	35·2
	24	R	36·3	36·2	36·1	35·8
	25	R	36·3	36·2	36·3	36·4
5 Prednisone	7	R	35·5	35·8	35·3	35·0
	14	R	35·4	36·0	36·0	36·0
	26	L	33·0	33·9	35·0	34·5

0·4 C.; in two knees it remained unchanged; in the remaining knee it fell by 0·4 C. In the cases showing fluctuations in the first 24 hours, there was a gradual return of the temperature towards the original level by the end of the fifth day. The most marked changes of intra-articular temperature occurred in the two cases receiving the inert aqueous vehicle.

Synovial fluid was obtained throughout the investigation from one knee joint of each control case, and included fluid from the two knees which had been injected with the inert aqueous vehicle. In every case it was clear and yellowish, and showed the high viscosity characteristic of osteo-arthritis (Ropes and Bauer, 1953). No obvious clinical change occurred in the viscosity of the fluid throughout the investigation. The highest initial white cell count was 1,060 per c.mm., the cells being predominantly mononuclear (Table III). It rose slightly in four cases in the first 24 hours, and had fallen towards or below the original level by the end of the fifth day. The highest rise did not occur in either of the cases which had received the inert aqueous vehicle and had undergone the maximum fluctuations of intra-articular temperature. In one case, which had shown no fluctuations in temperature in the first 24 hours, the white cell count actually fell slightly. The symptoms of stiffness after rest and pain in the knees were present in all the control patients. These symptoms were relieved in four patients, but relapsed completely by the fourth day (Table IV, opposite). In the two cases given the inert aqueous vehicle the same degree of relief appeared to occur in the knee which had been injected with the inert aqueous vehicle as in the opposite knee which had received no injection. In all cases the relief was noticed within 24 hours of the introduction of the needle for the preliminary test. In one case no change in symptoms occurred throughout the investigation.

TABLE III

SYNOVIAL FLUID CELL COUNTS

Group	Case No.	Knee	Before	After		
				24 hrs	48 hrs	5 days
1	1*	R	595	670	545	995
	2	R	325	290	490	470
	3	R	285	370	295	260
	4	L	1,060	1,665	110	40
	5*	R	485	505	250	150
2	8	R	375	3,490	1,720	150
	9	L	405	2,765	1,280	310
	10	R	505	685	190	150
3	5	R	360	685	570	100
4	24	R	1,125	1,170	1,530	1,060
	25	R	85	2,245	720	190
5	26	L	115	20	170	160

* Inert aqueous vehicle.

TABLE IV

RELIEF OF SYMPTOMS

Group	Case No.	Knee	Stiffness		Pain	
			Relief	Duration (days)	Relief	Duration (days)
1 Controls	1	R	Partial	4	Partial	4
		L	Partial	4	Partial	4
	2	R	Partial	3	Partial	3
	3	R	Nil		Nil	
	4	L	Partial	4	Partial	4
	5	R	Partial	3	Partial	3
		L	Partial	3	Partial	3
2 Hydrocortisone Acetate	1	L	Complete	10	Partial	7
	6	L	Complete	90	Complete	90
	7	R	Complete	14	Nil	
	8	R	Complete	9	Complete	9
	9	L	Complete	7	Complete	7
	10	R	Complete	21	Complete	28
	11	L	Nil		Nil	
	12	L	Complete	14	Complete	7
	13	R	Complete	21	Complete	21
	14	R	Nil		Nil	
	15	L	Partial	10	Partial	10
	16	R	Partial	7	Nil	
	17	R	Complete	21	Complete	21
	18	L	Partial	10	Nil	
	19	R	Complete	10	Complete	14
	20	R	Complete	7	Complete	7
3 Hydrocortisone Acetate	4	R	Complete	10	Complete	7
	5	R	Partial	10	Partial	10
4 Hydrocortisone Acetate	21	L	Partial	21	Partial	21
	22	L	Complete	7	Complete	7
	23	L	Complete	10	Complete	7
	24	R	Partial	14	Complete	21
	25	R	Complete	28	Complete	28
5 Prednisone	7	R	Complete	7	Partial	7
	14	R	Partial	7	Partial	7
	26	L	Complete	14	Partial	14

After Intra-Articular Injection of Hydrocortisone Acetate and Prednisone

The intra-articular temperature in the patients in all the groups studied was above 33° C., which is the upper limit for normal joints (Horvath and Hollander, 1949; Penneys and Smukler, 1956).

After the injection of hydrocortisone acetate (Fig. 2A, B, overleaf; Table II), the patients with generalized osteo-arthritis and the two males showed a rise in intra-articular temperature which varied from 0·5 to 2·1° C., the maximum rise occurring at the end of 24 hours but being delayed in three cases until the end of 48 hours. In ten of the sixteen patients with generalized osteo-arthritis who were followed for 5 days, the temperature had returned to the pre-injection level or below in seven, while in three it had not quite reached the pre-treatment level by that time.

In the Group 4 patients suffering from obesity (Fig. 2B, overleaf; Table II) there was no significant rise in the intra-articular temperature, and in two of these cases there was a significant fall of temperature below the pre-treatment level by the end of 48 hours. In all cases there was a tendency for the intra-articular temperature to return to or near the pre-treatment level.

Three cases of generalized osteo-arthritis which received injections of prednisone responded in a similar manner to those receiving hydrocortisone acetate, but in one case the intra-articular temperature had not begun to return to its original level by the fifth day (Table II).

Synovial fluid was obtained from three cases of generalized osteo-arthritis, one of the male patients, two of the cases suffering from obesity associated with arthritis, and from one of those receiving prednisone (Table III). As in the controls the fluid was clear, highly viscous, and produced a firm clot on addition of acetic acid. In four of the cases which had received hydrocortisone acetate, the white cell count rose significantly by the end of 24 hours, and these included one case where the intra-articular temperature had not changed throughout the investigation; in two other cases minor rises occurred. In five cases the cell count fell to or below the original level, as in the controls, while in one case it rose further by the end of 48 hours before falling below the pre-injection level. The fluid had

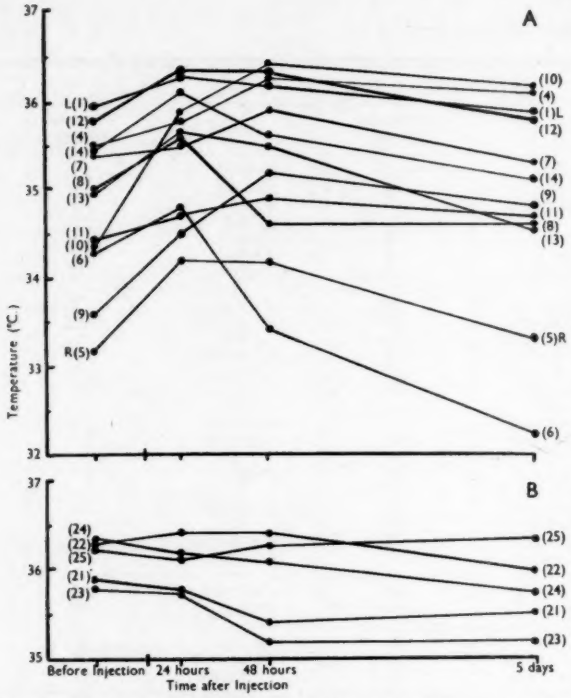


Fig. 2A.—Intra-articular temperature changes in Groups 2 and 3 before and after injection of hydrocortisone acetate.
Fig. 2B.—Intra-articular temperature changes in Group 4 before and after injection of hydrocortisone acetate.

in each case been aspirated as completely as possible on each occasion, and the ratio of polymorphonuclear cells to mononuclear cells remained below 25 per cent. throughout the investigation, suggesting that the rise in count affected in each case both types of cell. In the case which received the prednisone the count actually fell in 24 hours to rise again by the end of 48 hours. The significance of this finding is not known.

The response of the symptoms of stiffness and pain to injection of the knee with hydrocortisone acetate or prednisone is shown in Table IV. In 24 cases there was a definite improvement in, or disappearance of, stiffness; complete relief occurred in seventeen cases, partial relief in seven, and no change in two. Pain completely disappeared in fourteen patients, partially disappeared in seven, and remained unchanged in five (Table IV). The degree of relief of stiffness and pain experienced by an individual patient was not always the same, because in three cases stiffness in the knee was completely relieved, while pain was only partially relieved, and in one case stiffness was completely relieved while pain persisted unchanged. The shortest period of improvement of either symptom was 7 days from the commencement of the investigation and the longest period was 21 days, except in one case in which relief continued for 3 months.

Discussion

The observation that the intra-articular temperature is above normal in cases of osteo-arthritis is similar to that made by other investigators (Horvath and Hollander, 1949; Fletcher, Jacobs and Rose, 1954).

The significant post-injection rise of intra-articular temperature by the end of 24 hours in thirteen of sixteen cases of osteo-arthritis and in the two male cases, and the rise by the end of 48 hours in the three remaining cases of generalized osteo-arthritis, contrasts with the temperature changes which occurred in the group presenting with arthritis of the knees secondary to longstanding obesity. This seems to indicate that in the latter group the knee joint reacts differently to hydrocortisone acetate. The temperature changes also contrast sharply with those occurring in rheumatoid joints after the injection of intra-articular hydrocortisone acetate when a marked reduction in temperature consistently occurs (Hollander and others, 1951). It appears that the temperature changes occurring in the knee joint in response to hydrocortisone depend on the type of joint condition present.

Irritation of the joint by the needle could possibly produce the rise in temperature found in generalized osteo-arthritis and in the two males, but the fluctuations were greater than those found in the control series and in the obesity groups, indicating that this cannot be the whole explanation. In a series of cases to which intra-articular procaine was administered a similar conclusion was reached (Fletcher and others, 1954).

Transient inflammatory response to the hydrocortisone might conceivably be responsible for the fluctuations in intra-articular temperature, but the clinical condition of the joints never deteriorated, and in most cases the symptoms improved, the viscosity of the fluid did not change clinically, and the white cell count, although it rose in a number of cases, was always predominantly mononuclear and was never found in the range associated with septic arthritis or rheumatoid arthritis.

That vascular changes in the intra-articular structures of the knee accompany changes in joint temperature is suggested by the observation that, in normal individuals, body-heating regularly causes a rise in joint temperature accompanying the rise in skin temperature (Penneys and Smukler, 1956), and plethysmographic studies have also suggested that the blood flow in the normal knee joint changes

rapidly as the intra-articular temperature rises from 30 to 40° C. (Bonney, Hughes, and Janus, 1952). Pathological investigations of the osteo-arthritic hip have indicated that the vascular pattern in the bone is increased (Harrison, Schajowicz, and Trueta, 1953), suggesting that changes in blood flow are possible in the joint structures in this condition. It may be, therefore, that the changes in joint temperature indicate changes in joint blood flow, but the ultimate proof of this would depend on other methods of study such as plethysmography. In any event, the mechanism of action of hydrocortisone in generalized osteo-arthritis cannot be the simple anti-inflammatory mechanism that has been shown to operate in rheumatoid arthritis (Hollander and others, 1951).

The synovial fluid viscosity and mucin clot formation remained clinically unchanged throughout the investigation, and the white cell counts were well within the limits usually found in osteo-arthritis. That the white cell count rose in four of five controls in the first 24 hours, as well as in the cases receiving hydrocortisone acetate, suggests that a mechanical factor was responsible. Because the proportion of polymorphonuclear cells to monocytes in the fluids remained the same, the changing cell counts may simply be related to the re-accumulation of fluid after complete aspiration of the joints.

Of the two symptoms, stiffness and pain, which troubled the patients, stiffness was more consistently relieved than pain, although in the majority of cases relief was approximately of the same duration for each symptom. It had been hoped to find a relationship between alleviation of these symptoms and changes in the intra-articular temperature accompanying injection of either hydrocortisone acetate or prednisone. However, the response of each symptom to the introduction of the needle into the knee joint was influenced by the knowledge that a special procedure was being used, even in the control group, and although relief was of considerably shorter duration in the controls than in the other groups the observation points again to the care which must be exercised in assessing results of any treatment on a purely symptomatic basis.

This study shows that significant changes in intra-articular temperature occur in the knee joints of patients with generalized osteo-arthritis, and that alterations in the symptoms are not entirely dependent on these changes.

Summary

A study has been made in 26 cases of osteo-arthritis of the response to intra-articular injections of hydrocortisone acetate and prednisone into the knee joint.

The cases were divided into one group of controls, and three groups of patients with generalized osteo-arthritis, traumatic arthritis, and obesity associated with arthritis. Joint temperature studies were carried out before and after the intra-articular injections.

The results indicate that the initial joint temperature is higher in these cases than in normal subjects and that it rises after intra-articular injections in some of the groups but not in others; this suggests a difference in the response of the joints to therapy, and contrasts with the changes which occur in the joints of patients with rheumatoid arthritis in similar circumstances.

The relief of the symptoms of pain and stiffness in the joints does not appear to be directly related to the intra-articular temperature changes.

REFERENCES

Bonney, G. L. W., Hughes, R. A., and Janus, O. (1952). *Clin. Sci.* **11**, 167.

Fletcher, E., Jacobs, J. H., and Rose, C. F. (1954). *Ann. phys. Med.*, **2**, 123.

Harrison, M. H. M., Schajowicz, F., and Trueta, J. (1953). *J. Bone Jt Surg.*, **35B**, 598.

Hollander, J. L. (1953). "Comroe's Arthritis", 5th ed. Lea and Febiger, Philadelphia.

——, Stoner, E. K., Brown, E. M., and De Moor, P. (1951). *J. clin. Invest.*, **30**, 701.

Horvath, S. M., and Hollander, J. L. (1949). *Ibid.*, **28**, 469.

Kellgren, J. H., and Moore, R. (1952). *Brit. med. J.*, **1**, 181.

Penneys, R., and Smukler, N. M. (1956). *Annals of the Rheumatic Diseases*, **15**, 241.

Ropes, M. W., and Bauer, W. (1953). "Synovial Fluid Changes in Joint Disease." Harvard University Press, Cambridge, Mass.

Young, H. H., Ward, L. E., and Henderson, E. D. (1954). *J. Bone Jt Surg.*, **36A**, 605.

Etude de l'ostéo-arthrite à l'aide de la réponse thermique intra-articulaire à l'injection d'acétate d'hydrocortisone et de prednisone

RÉSUMÉ

On étudia dans 26 cas d'ostéo-arthrite la réponse à des injections d'acétate d'hydrocortisone et de prednisone dans l'articulation du genou.

Les cas furent divisés en un groupe témoin et trois groupes de malades atteints d'ostéo-arthrite généralisée, d'arthrite traumatique et d'obésité associée à l'arthrite. La température articulaire fut déterminée avant et après les injections intra-articulaires.

Les résultats montrent que la température initiale de l'articulation est plus élevée dans ces cas que chez des sujets normaux, et qu'elle s'élève après les injections intra-articulaires dans certains des groupes mais pas dans d'autres; ceci suggère une différence dans la réponse des articulations au traitement, et contraste avec les altérations qui se produisent dans les articulations de malades atteints d'arthrite rhumatismale dans des circonstances semblables.

Le soulagement des symptômes de douleur et de raideur articulaires ne semble pas être en relation directe avec les variations de la température intra-articulaire.

Estudio de la osteo-artritis con la ayuda de la respuesta térmica intra-articular á inyecciones de acetato de hidrocortisona y de prednisona.

SUMARIO

En 26 cases de osteo-artritis se estudió la respuesta á inyecciones de acetato de hidrocortisona y de prednisona en la articulación de la rodilla.

Los casos fueron repartidos entre un grupo de control y tres grupos de enfermos con osteo-artritis generalizada, artritis traumática y obesidad asociada a la artritis. La temperatura articular fué medida antes y después de las inyecciones intra-articulares.

Los resultados muestran que la temperatura inicial de la articulación es mayor en estos casos que en sujetos normales, aumentando después de las inyecciones intra-articulares en ciertos grupos, pero no en otros; esto sugiere una diferencia en la respuesta de las articulaciones al tratamiento, y contrasta con las alteraciones que se producen en las articulaciones de enfermos con artritis reumatoide en circunstancias semejantes.

El alivio sintomático del dolor y de la rigidez articulares no parece relacionarse directamente con las variaciones de la temperatura intra-articular.

Ann. rheum. Dis. (1956), **15**, 327.

ABSORPTION OF HYDROCORTISONE FROM THE JOINT CAVITY INTO THE CIRCULATION

BY

MARTTI OKA

From the Medical Department, Kivelä Hospital, Helsinki

(RECEIVED FOR PUBLICATION AUGUST 2, 1956)

Intra-articular hydrocortisone therapy has been in extensive use for approximately 5 years. It has been stated that this therapy is strictly for local palliation and has no systemic effects (Hollander, 1953). Local hydrocortisone therapy is especially recommended in cases in which the systemic use of cortisone is contra-indicated on general medical grounds (Kersley, 1953).

On the other hand, Young, Ward, and Henderson (1952) noted clinically systemic as well as local effects after intra-articular injections of hydrocortisone acetate in 31 (21 per cent.) of their 148 patients. There was clinical improvement in involved but uninjected joints in this group, the effect being similar in nature, both subjectively and objectively, to that which results from the oral or intramuscular administration of cortisone. Its occurrence indicates that at least part of the hydrocortisone acetate injected into the synovial cavity is absorbed into the blood stream and reaches the general circulation.

In a study of the intra-articular metabolism of hydrocortisone and cortisone (Wilson, Fairbanks, McEwen, and Ziff, 1955), it was found that hydrocortisone acetate disappeared rapidly from the synovial fluid after intra-articular injection. After 1 hour and 3 hours, 86 and 97 per cent. respectively had disappeared. Appreciable amounts of what was most probably hydrocortisone was found by paper chromatography 30 minutes after the intra-articular injection in the contralateral uninjected knee, indicating that a large proportion of the injected hormone entered the circulation unchanged and also escaped metabolism in the liver during the first 30 minutes after injection.

The aim of the present investigation has been to study the absorption of hydrocortisone acetate from the joint cavity into the blood by measuring the free plasma 17-hydroxycorticosteroids under experimental conditions in which the endogenous output of hydrocortisone had been eliminated. The suppression of the endogenous hydrocortisone was made possible by administering $\triangle^1$-9-α-fluoro hydrocortisone ($\triangle$FF). Liddle (1956) has shown that $\triangle$FF is so effective in suppressing the secretion of corticotropin that relatively minute doses of this steroid will reduce the blood 17-hydroxycorticosteroid level almost to zero. Subsequently, for as long as this suppressive dose is maintained, one may consider any appreciable rise in the 17-hydroxycorticosteroid level to be the result of some additional treatment, *e.g.* the administration of either steroids or corticotropin.

Material and Methods

The free plasma 17-hydroxycorticosteroids were determined by the method of Silber and Porter (1954) as modified by Peterson, Wyngaarden, Guerra, Brodie, and Bunim (1955). In this laboratory the average plasma 17-hydroxycorticosteroid level of normal adults was 13 μg./100 ml. with a range of from 7 to 21 μg./100 ml.

In this study 0·5 mg. $\triangle$FF* was administered orally every 6 hours for 2 days before the intra-articular or oral administration of hydrocortisone acetate. The administration of $\triangle$FF was continued until the last blood specimen had been drawn.

The absorption of intra-articularly injected hydrocortisone acetate into the blood was studied in six patients suffering from rheumatoid arthritis or osteo-arthritis of the knees. The first blood specimen was drawn immediately before the intra-articular injection of the steroid, and blood specimens were then drawn at varying intervals.

One patient receiving a single oral dose of hydrocortisone acetate served as a control.

* The $\triangle^1$-9-α-fluoro hydrocortisone used in these experiments was kindly supplied by Dr. C. J. O'Donovan of the Upjohn Company.

Results

The results are presented in the Table and the Figure. It can be seen that △FF reduced the initial plasma 17-hydroxycorticosteroid levels almost to zero in six instances. In two instances (Cases 5 and 6), the values were the same as the lower limit of the normal range.

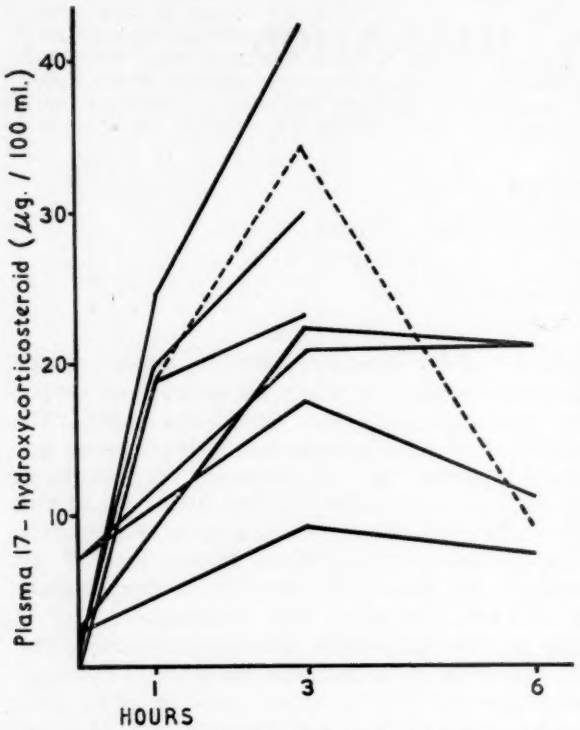


Figure.—Plasma 17-hydroxycorticosteroid levels after intra-articular (————) or oral (- - - - - - -) administration of hydrocortisone acetate.

Intra-articular hydrocortisone acetate injection produced a strong rise in the plasma 17-hydroxycorticosteroid level in all cases except one (Case 3). The highest levels were obtained 3 hours after the intra-articular injection. 24 hours after the injection the values had decreased almost to the initial levels. The rate of absorption seems to be very individual. 25 mg. hydrocortisone acetate produced a stronger elevation of plasma 17-hydroxycorticosteroids in one patient (Case 6) than was produced by a dose of 100 mg. in another (Case 3).

25 mg. hydrocortisone acetate orally produced an elevation of plasma 17-hydroxycorticosteroids comparable to that produced by 100 mg. intra-articularly. Here, too, the top level was reached 3 hours after ingestion of the tablet. The plasma 17-hydroxycorticosteroid values 6 hours after the administration of the steroid showed a sharper decrease in the case in which hydrocortisone acetate was given orally.

Discussion

The results of these experiments show that intra-articularly injected hydrocortisone acetate is absorbed into the circulation to a considerable degree.

The plasma 17-hydroxycorticosteroid levels after intra-articular hydrocortisone acetate injections are so high that systemic hormonal effects can be expected if large and frequent doses are used.

Summary

The absorption of hydrocortisone acetate from the joint cavity into the circulation has been studied under experimental conditions in which the endogenous output of hydrocortisone was blocked by the administration of △[1]-9-α-fluoro hydrocortisone.

High plasma 17-hydroxycorticosteroid values were obtained after the intra-articular injection of 25 to 100 mg. hydrocortisone acetate.

TABLE

PLASMA 17-HYDROXYCORTICOSTEROID LEVELS AFTER INTRA-ARTICULAR OR ORAL ADMINISTRATION OF HYDROCORTISONE ACETATE TO RHEUMATIC SUBJECTS. THE ENDOGENOUS HYDROCORTISONE OUTPUT WAS BLOCKED BY △[1]-9-α-FLUORO HYDROCORTISONE

Case No.	Diagnosis	Dose (mg.)	Route	Plasma 17-hydroxycorticosteroids (μg./100 ml.) after Administration of Hydrocortisone Acetate (hrs)				
				0	1	3	6	24
1	Rheumatoid arthritis	100	intra-articular	0	18	23	—	—
2	Rheumatoid arthritis	100	intra-articular	0	24	42	—	—
3	Osteo-arthritis	100	intra-articular	2	—	9	7	5
4	Rheumatoid arthritis	100	intra-articular	0	20	30	—	—
4	Rheumatoid arthritis	50	intra-articular	2	—	22	21	6
5	Osteo-arthritis	50	intra-articular	7	—	17	11	9
6	Rheumatoid arthritis	25	intra-articular	7	—	21	21	5
7	Rheumatoid arthritis	25	oral	1	19	34	9	—

My thanks are due to Dr. Juha Kytilä for drawing the blood samples.

REFERENCES

Hollander, J. L. (1953). *Ann. intern. Med.*, **39**, 735.
Kersley, G. D. (1953). "VIII Congrès International des Maladies Rhumatismales." Summary of Communications, p. 34.
Liddle, G. W. (1956). *J. clin. Endocr.*, **16**, 557.
Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J. (1955). *J. clin. Invest.*, **34**, 1779.
Silber, R. H., and Porter, C. C. (1954). *J. biol. Chem.*, **210**, 923.
Wilson, H., Fairbanks, R., McEwen, C., and Ziff, M. (1955). *Ann. N.Y. Acad. Sci.*, **61**, Art. 2, p. 502.
Young, H. H., Ward, L. E., and Henderson, E. D. (1952). *J. Bone Jt Surg.*, **36A**, 602.

Absorption de l'hydrocortisone de la cavité articulaire dans la circulation

RÉSUMÉ

L'absorption d'acétate d'hydrocortisone de la cavité articulaire dans la circulation a été étudiée dans des conditions expérimentales dans lesquelles la production endogène d'hydrocortisone fut bloquée par l'administration de Δ^1-9-α-fluoro hydrocortisone.

On obtint des chiffres sanguins élevés de 17-hydroxycorticostéroïde après l'injection intra-articulaire de 25 à 100 mg. d'acétate d'hydrocortisone.

Absorpción de la hidrocortisona de la cavidad articular en la circulación

SUMARIO

La absorpción de acetato de hidrocortisona de la cavidad articular en la circulación fué estudiada en condiciones experimentales en las cuales la producción endógena de hidrocortisona fué bloqueada por la administración de Δ^1-9-α-fluoro hidrocortisona.

Se obtuvieron cifras sanguíneas altas de 17-hidroxicorticoesteroide después de la inyección intra-articular de 25 a 100 mg. de acetato de hidrocortisona.

Ann. rheum. Dis. (1956), **15**, 330.

LOCAL INJECTION OF HYDROCORTISONE AND PROCAINE IN OSTEO-ARTHRITIS OF THE HIP JOINT

BY

V. M. LEVEAUX AND C. E. QUIN
Arthur Stanley Institute, Middlesex Hospital, London

(RECEIVED FOR PUBLICATION JULY 30, 1956)

The local injection of therapeutic substances to relieve symptoms in osteo-arthritis has long been a controversial method of treatment. Desmarais (1952) reviewed the use of various substances, including procaine lactic acid, acid potassium phosphate, and procaine. He further critically examined the results of his own series of 189 injections into hip or knee joint with alkaline procaine, lactic acid, saline, or needle prick alone. There appeared to be little difference between the results with these various materials, except that procaine gave slightly more pain relief and was probably the substance of choice.

The introduction of hydrocortisone (Compound F) stimulated further studies in relation to osteo-arthritis of the hip joint. Hollander, Brown, Jessar, and Brown (1951) reported the responses of two patients suffering from unilateral osteo-arthritis of the hip to the injection of 25 mg. hydrocortisone into the region of the affected joint. They stated that "a prompt alleviation of symptoms and improvement in range of motion was noted in both patients after 24 hours; this persisted for 7 days in one and 13 days in the other". Two years later Hollander (1953) was able to report on 77 injections into osteo-arthritic hips, in which relief was obtained for at least 3 days in 47 per cent. of cases.

Approach to the Hip Joint

The majority of workers have approached the joint anteriorly, a method which Dobson (1950) found to be successful in 67 per cent. of a cadaver series.

Landsmeer and Koumans (1954) described an approach from the caudo-lateral aspect. In this method the needle is inserted at a point up to 5 cm. caudal to the base of the greater trochanter and is directed upwards towards a point on the middle third of a line between the anterior-superior iliac spine and the pubic tubercle. By this means the needle passes over the anterior aspect of the femoral neck to be arrested by the caudal aspect of the femoral head. At this point the needle should be within the joint space.

Clearly the injection of a deeply-placed joint like the hip joint can never be as straightforward a procedure as that of an accessible joint such as the knee. Nevertheless, this method of injection was found to be generally satisfactory in the present series, and less of an ordeal for the patient than the anterior approach since the sensitive groin area was avoided. A 4-in. 20 B.W.G. needle was adequate for most cases, but in a few large or obese subjects a 6-in. 18 B.W.G. needle was used.

Fig. 1 (opposite) shows the patient with skin markings delineated, including the anterior part of the iliac crest and the greater trochanter. The two vertical lines in the groin represent the limits of the middle third of the line between the anterior-superior iliac spine and the pubic tubercle. The needle is passing through anaesthetized skin and shows the general direction of aim. Fig. 2 (opposite) shows an *x*-ray film of an injection into the opposite hip of the patient shown in Fig. 1.

Fig. 3 (overleaf) shows the relationship of the surface markings rendered visible by overlying copper wire to the hip joint and injecting needle. Fig. 4 (overleaf) illustrates a practical snag, the needle point being arrested by the inter-trochanteric line.

This caudo-lateral approach was used throughout the present series.

Present Investigation

The object of the investigation was to compare the effect of an injection of 5 ml. 2 per cent. procaine (Injection "P") with that of a combined injection of 50 mg. hydrocortisone and 5 ml. 2 per cent. procaine (Injection "H").

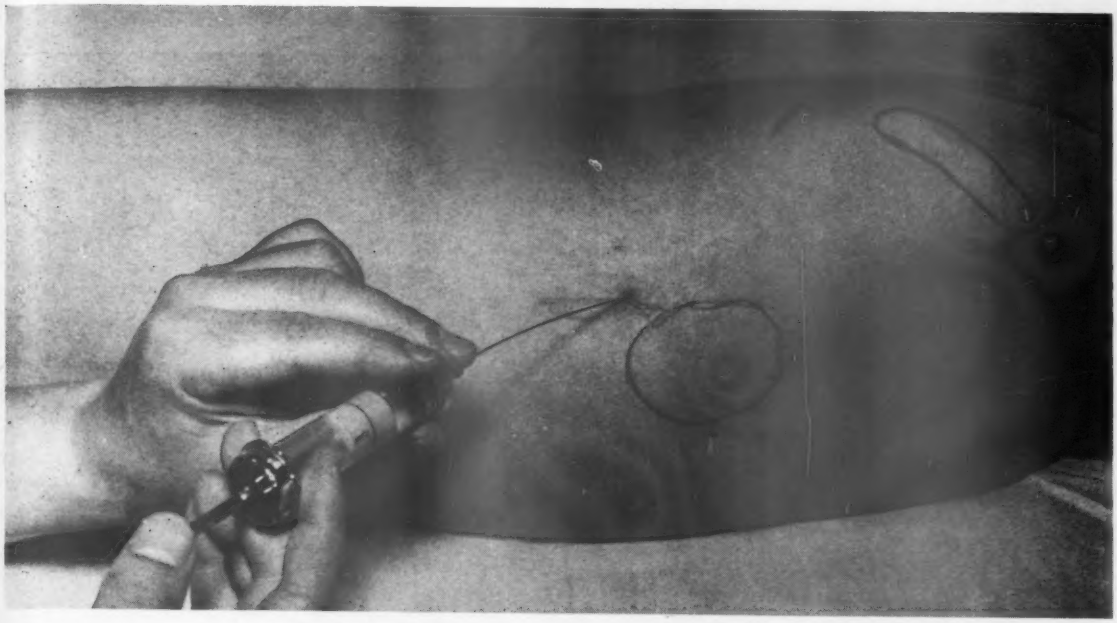


Fig. 1.—Surface markings delineated and insertion of needle.

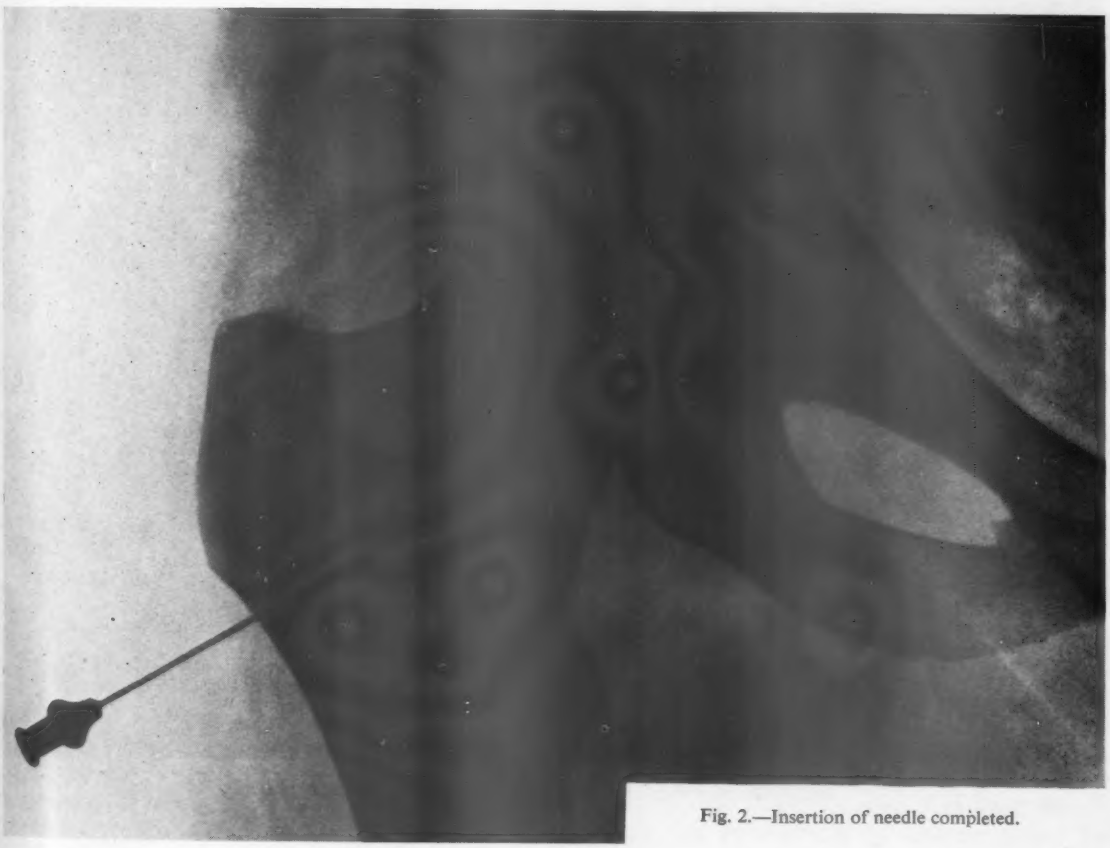


Fig. 2.—Insertion of needle completed.

Fig. 3.—Relationship of the surface markings to hip joint and needle.

Fig. 4.—Needle arrested by inter-trochanteric line, a practical snag.

Thirty patients were divided into two groups of fifteen. In Group I, Injection "P" was given first, and later, when any benefit obtained had worn off, Injection "H" was given. In Group II the order of injection was reversed. The patients were not informed of any difference between the two injections.

Each patient was assessed immediately before the injection and again one week after. Thereafter observation was maintained until it was evident that any benefit obtained had worn off.

The chief measure of benefit was that of pain relief. In addition the distance between the medial malleoli on full abduction of the legs was made and the time taken to walk ten times the length of a 35-foot corridor were recorded. Both these measurements were taken immediately before and one week after the injection.

Radiological Classification of Severity of Disease.—The cases were allotted to the following broad groups:

0. No radiological change (four joints showed no radiological change but on clinical grounds were considered to be osteo-arthritic).
1. Slight loss of cartilage space. Early new bone formation.
2. Moderate loss of cartilage space. Moderate new bone formation. Subchondral sclerosis. Lipping. Early cyst formation. Periosteal new bone along neck of femur.
3. Severe or complete loss of cartilage space. Deformity of femoral head. Marked cyst formation. Gross new bone formation.

A simple addition of the Group numerals in each joint injected gives an empirical measure of the severity of involvement in Groups I and II. In

some patients with clinical bilateral disease, the second injection was sometimes given into the opposite joint from the first, so a separate addition is made for Injections "P" and "H" in each Group.

Summary of Results

The results are set out in detail in Tables I and II. The results of the first injection show a marked similarity in the effect of Injections "P" and "H". Relief was obtained in eleven of the fifteen cases in each group after the first injection. Injection "P", however, produced a longer average period of relief, namely 3·07 weeks per patient (Table I) as compared with 1·6 weeks (Table II). Injection "P" diminished the average time over the standard course by 18·3 sec. (Table I) and Injection "H" by 10·8 sec. (Table II). On radiological assessment the groups were comparable, having an empirical total of 31 for Injection "P" in Group I and 33 for Injection "H" in Group II. Therefore, on the evidence of the first injection alone, Injection "P" would seem to be superior to Injection "H" in duration of benefit and increase in mobility.

The results of the second injection were in marked contrast to those of the first. Injection "P" relieved only one case, whereas Injection "H" relieved thirteen cases. Ten cases were made worse by Injection "P" as compared with one by Injection "H". The average duration of benefit was 0·057 weeks with Injection "P" and 2·5 weeks with Injection "H". In the Injection "P" patients, the time over the standard course was actually increased by an average of 12·3 seconds, whereas with Injection "H", it was reduced by an average of 7·3 seconds. The radiological assessment of the severity of disease gave an empirical total of 34 with Injection "H" in Group I and 33 with Injection "P" in Group II.

As regards objective measurement of hip movement represented by the intermalleolar distance on full abduction in this series no definite change was

TABLE I

GROUP

Injection	Case	Pain	Degree of Relief	Duration of Benefit (wks)	Difference in Times on Course (sec.)	Radiological Severity*		Intermalleolar Distance (in.)	
						Right	Left	Before	After
(1) Procaine alone	A	Less	Slight	5	Not done	3	*3*	9	10
	B	Less	Slight	3	−15	*3*	0	23	25
	C	More	—	—	Not done	Old operation	*1*	24½	23
	D	Less	Moderate	6	− 6	0	*0*	17	22
	E	Less	Slight	3	−38	*2*	2	12	13
	F	Same	—	—	− 2	1	*3*	32	30½
	G	Less	Moderate	7	+ 9	*1*	3	22	21
	H	Less	Moderate	6	−20	*2*	0	22	23½
	I	Less	Marked	4	−53	*3*	3	11	11
	J	Less	Moderate	2	−33	2	*2*	15	14
	K	Less	Slight	2	−27	*3*	0	16½	15
	L	Less	Marked	2	−35	*2*	0	20	17
	M	Less	Slight	6	+10	*2*	2	9	8
	N	More	—	—	0	*3*	0	15	13
	O	Same	—	—	−28	*1*	0	28	24
	Average			3·07	−18·3	*Total 31 in hips injected (italics)			
(2) Hydrocortisone + Procaine	A	Less	Marked	2	−10	*3*	3	9	8
	B	Less	Slight	3	− 4	*3*	0	25	25
	C	Less	Moderate	4	Not done	Old operation	*1*	23	19
	D	Less	Marked	2 days	Same	0	*0*	19	20
	E	Less	Moderate	8	−23	*2*	2	12½	11½
	F	Less	Marked	3	−21	1	*3*	30½	30½
	G	Less	Marked	3	− 5	1	*3*	27	27
	H	Same	—	—	− 3	*2*	0	23½	22
	I	Less	Moderate	4	− 9	3	*3*	10	9
	J	Less	Moderate	2½	+13	*3*	3	14	14
	K	Less	Moderate	1	−20	*3*	0	14	15
	L	More	—	—	+14	*2*	0	17	18
	M	Less	Slight	4	−10	*2*	2	11	10
	N	Less	Slight	5 days	−19	*3*	0	13	11
	O	Less	Moderate	2	+ 5	*1*	0	24	27
	Average			2·5	− 7·3	*Total 34 in hips injected (italics)			

TABLE II

GROUP II

Injection	Case	Pain	Degree of Relief	Duration of Benefit (wks)	Difference in Times on Course (sec.)	Radiological Severity*		Intermalleolar Distance (in.)	
						Right	Left	Before	After
(1) Hydrocortisone + Procaine	P	Less	Moderate	2	−21	*3*	0	19½	19½
	Q	Less	Marked	2	− 3	0	*3*	24	23½
	R	More	—	—	− 1	*3*	0	32	32½
	S	Less	Moderate	3	+27	*3*	2	11	10
	T	Less	Slight	1	+ 7	*3*	3	14	13½
	U	Same	—	—	+ 6	*1*	0	38	41½
	V	Less	Slight	2	−23	3	*2*	4	6
	W	Less	Moderate	2	− 1	0	*2*	25½	26
	X	Same	—	—	− 8	0	*1*	27	27
	Y	Less	Slight	1½	−61	*3*	2	13	12½
	Z	Less	Marked	1	−34	2	*3*	16½	16½
	A2	Same	—	—	+13	*0*	1	36	35½
	B2	Less	Moderate	4	− 1	*1*	0	29	27½
	C2	Less	Moderate	1½	+ 6	*3*	2	25½	25
	D2	Less	Slight	4	−68	*2*	3	12½	13½
	Average			1·6	−10·8	*Total 33 in hips injected (italics)			
(2) Procaine alone	P	More	—	—	+34	*3*	0	19	19½
	Q	More	—	—	Same	0	*3*	22½	21½
	R	More	—	—	+10	*3*	0	32	32
	S	More	—	—	− 5	*3*	2	8½	9½
	T	Same	—	—	+20	3	*3*	14	13½
	U	Same	—	—	+ 1	*1*	0	41½	41
	V	More	—	—	−17	3	*2*	5	6
	W	More	—	—	−12	0	*2*	22½	24
	X	More	—	—	− 4	0	*1*	27	26½
	Y	More	—	—	+76	*3*	2	13	11
	Z	More	—	—	+45	2	*3*	16½	14½
	A2	Same	—	—	− 3	*0*	1	37	35
	B2	More	—	—	− 1	*1*	0	27½	32
	C2	Same	—	—	+26	*3*	2	25	24
	D2	Less	Moderate	6 days	+15	*2*	3	13	12
	Average			0·057	+12·3	Total 33 in hips injected (italics)			

TABLE III

SUMMARY OF RESULTS IN GROUPS I AND II

Group	I				II			
Injection	(1) Procaine alone		(2) Hydrocortisone + Procaine		(1) Hydrocortisone + Procaine		(2) Procaine alone	
Results	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Relief (Marked, Moderate, Slight)	2, 4, 5 } 11	73·3	4, 6, 3 } 13	86·7	2, 5, 4 } 11	73·3	0, 1, 0 } 1	6·7
No Change	2	13·3	1	6·7	3	20·0	4	26·7
More Pain	2	13·3	1	6·7	1	6·7	10	66·6

noted. This figure, however, gives a clinical guide to the severity of the mechanical disability produced by the disease.

Discussion

It is difficult to explain this marked difference between the first and second injections on a purely organic basis. The technique used was apparently the same in each case, any inadequacy in method being applicable to each group equally.

The psychological response to a new and rather dramatic form of treatment cannot be overlooked, and makes evaluation of a first injection with any therapeutic substance difficult. Probably second and subsequent injections are necessary before the real worth of the procedure can be appreciated.

Our observations on patients in this series, and our experience in other cases, leads us to believe that procaine alone is far inferior to the combined hydrocortisone and procaine injection, and frequently causes an increase in pain. The combined

injection, on the other hand, does appear to be of definite value as a palliative measure in the treatment of osteo-arthritis of the hip. The patients have usually had many forms of treatment without much benefit, and to them the relief of pain following the combined injection has been most welcome. Not least of all a few comfortable nights in bed, with changes of position proving relatively painless, are encouraging. This relief of symptoms can often be obtained again by a further injection when it becomes necessary.

The method of injection used in this series is not difficult, nor is it a great ordeal for the average patient. In sensitive patients with a dread of the needle, however, this treatment is probably better avoided. The results obtained compare favourably in our experience with the usual methods of physical treatment employed for osteo-arthritis of the hip.

It must be emphasized, however, that this form of treatment is only a palliative measure, and that there are no grounds for believing that repeated injections will in any way alter the course of the disease. Nevertheless, injection of hydrocortisone with procaine may be of great value in helping a patient over a particularly painful episode. Surgical procedures in selected cases offer the best chance of obtaining a lasting relief of pain in osteo-arthritis of the hip. In our opinion injections of hydrocortisone with procaine have a part to play in the management of those patients in whom operation is not considered advisable, or who have to face a waiting period before operation.

Summary

Using the caudo-lateral approach in cases of osteo-arthritis of the hip joint, a comparison was made between an injection of 5 ml. 2 per cent. procaine and a combined injection of 50 mg. hydrocortisone and 5 ml. 2 per cent. procaine. Fifteen patients received the procaine alone first, and the combined injection subsequently, when all benefit of the first had worn off. Fifteen patients received the injections in the reverse order.

The results of the first injection in each group were remarkably similar as regards relief of pain and increase of mobility. The results of the second injection were very different and showed procaine alone to be markedly inferior to the combined hydrocortisone and procaine injection.

The influence of psychological factors on the response to first injections is emphasized, and the value and limitations of the combined injection are discussed.

It is concluded that procaine and hydrocortisone combined are of value as palliative substances used by local injection into the region of a painful osteo-arthritic hip joint.

We wish to acknowledge the helpful advice and encouragement given to us by Dr. Oswald Savage and Dr. A. C. Boyle throughout this work, and to thank Miss A. E. Bartholomew and Miss Y. V. Townshend for their assistance. We should also like to thank Dr. I. Yentis for help in the radiological grading of the cases.

REFERENCES

Desmarais, M. H. L. (1952). *Annals of the Rheumatic Diseases* **11**, 277.

Dobson, M. M. (1950). *Ibid.*, **9**, 237.

Hollander, J. L. (1953). *J. Bone Jt Surg.*, 35A, 983.

——, Brown, E. M., Jessar, R. A., and Brown, C. Y. (1951). *J. Amer. med. Ass.*, **147**, 1629.

Landsmeer, J. M. F., and Koumans, A. K. J. (1954). *Annals of the Rheumatic Diseases*, **13**, 246.

Injections locales d'hydrocortisone et de procaïne dans l'ostéo-arthrite de la hanche

RÉSUMÉ

En utilisant une approche caudo-latérale dans des cas d'ostéo-arthrite de la hanche, on compara l'injection de 5 cc. de procaïne à 2% et l'injection combinée de 50 mg. d'hydrocortisone et de 5 cc. de procaïne à 2%. Quinze malades reçurent d'abord la procaïne seule, puis l'injection combinée, après que tout bénéfice dû à la première eut disparu. Quinze malades reçurent les injections dans l'ordre inverse.

Les résultats de la première injection, dans chaque groupe, furent remarquablement semblables en ce qui concerne le soulagment de la douleur et l'augmentation de la mobilité. Les résultats de la seconde injection furent très différents et montrèrent que la procaïne seule était nettement inférieure à la combinaison procaïne-hydrocortisone.

L'influence des facteurs psychologiques sur la réponse aux premières injections est soulignée, et la valeur et les limites des injections combinées sont discutées.

On conclue que la procaïne et l'hydrocortisone sont utiles comme substances palliatives en injection locale dans la région d'une hanche ostéo-arthritique douloureuse.

Inyecciones locales de hidrocortisona y de procaina en la osteo-artritis de la cadera

SUMARIO

Empleando el acceso caudo-lateral en casos de osteo-artritis de la cadera, se compararon las inyecciones de 5 cc. de procaina a 2% con las inyecciones combinadas de 50 mg. de hidrocortisona y de 5 cc. de procaina a 2%. Quince enfermos recibieron al principio la procaina sola y luego, al desaparecer enteramente el beneficio de la primera inyección, la inyección combinada. Otros quince enfermos recibieron las inyecciones en el orden inverso.

Los resultados de la primera inyección fueron, en ambos grupos, señaladamente parecidos respecto al alivio del dolor y el aumento de la movilidad. Los resultados de la segunda inyección fueron muy diferentes y mostraron que la procaina sola fué netamente inferior a la procaina-hidrocortisona combinadas.

Se subraya la influencia de los factores sicológicos sobre la respuesta a las primeras inyecciones y se discuten el valor y los límites de las inyecciones combinadas.

Se concluye que la procaina y la hidrocortisona son paliativos útiles en inyecciones locales en la región de la cadera osteo-artrítica dolorosa.

Ann. rheum. Dis. (1956), **15**, 338.

LABORATORY AIDS IN STEROID THERAPY

BY

J. H. GLYN

Arthur Stanley Institute, Middlesex Hospital

(RECEIVED FOR PUBLICATION AUGUST 18, 1956)

Introduction

Cortisone and its analogues have been available in Great Britain for about 6 years. Despite extensive experience, it has not yet been possible to codify precisely either the indications for using these drugs or the method of regulating their dosage for maintenance therapy in the chronic rheumatic diseases. Nevertheless, the success or failure of treatment frequently depends on the refinements of these two factors.

The problem is complicated by the fact that several of the traditional and objective criteria of disease activity are not relevant when using the steroid drugs. For example, Vaughan, Bayles, and Favour (1951) wrote: " . . . It will be wiser to use the sedimentation rate in parallel with the eosinophil count merely as an index of continued hormonal activity and not as a criterion of the effectiveness of therapy or disease activity." Bagnall (1951) reported a rise in the sedimentation rate of twelve patients, all of whom showed undoubted clinical improvement. Copeman and others (1952) further emphasized the unreliability of this test " . . . except as an indication of general trends". These workers have also pointed out that the degree of anaemia, as represented by the haemoglobin concentration, may no longer be used as a measure of disease activity. It may be profoundly influenced, especially in the early stages of treatment, by irrelevant and pharmacologically-induced phenomena.

It is also true that these drugs invalidate several *clinical* criteria of the progress of the disease. For example, a gain in weight in a patient under treatment may be an ominous warning of sodium retention rather than an encouraging sign of diminished toxicity, and the suppression of a fever has to be interpreted quite differently from the occurrence of the same physical sign in an untreated patient.

The prognosis of rheumatoid arthritis is notoriously unpredictable. Since it is generally agreed that these powerful drugs should only be employed in patients in whom the disease might otherwise run a progressive or crippling course, there is, to quote Ragan, Demartini, Lamont-Havers, Jessar, Vaillancourt, and Grokoest (1952): " . . . a crying need for some definitive index of a poor prognosis early in the disease. If this were available, the tools are at hand to prevent invalidism at least for some years".

The investigation here reported was designed to overcome some of these difficulties. It was also hoped to throw some light on the vexed problem of knowing when steroid therapy can be safely terminated. It is often difficult to know the extent to which the disease has gone into a natural remission as opposed to a drug-induced remission. A premature withdrawal of the drugs may have serious consequences which are difficult to reverse. Finally, it was hoped that one or more of these tests might prove helpful in "screening" the new drugs which are launched on to the market each year and for which "anti-rheumatic" properties are claimed.

Material

During the last few years a large number of non-specific serological anomalies have been described in association with inflammatory or necrotic processes. They have been generically labelled "acute phase reactions", and claims have been made that fluctuations in the level of several of them run parallel to the severity of the conditions which provoked them. A selection of these tests was applied to seventy patients suffering from various collagen vascular diseases in whom anomalous situations had arisen either during or after steroid therapy. In eight of these patients, the tests were performed serially during the first few months of receiving these drugs. It is this group whose results are analysed below.

Only one major criterion was used in selecting the tests to be studied, namely that they should be sufficiently simple to be used routinely if they proved helpful. The tests selected on this basis are listed in Table I (opposite).

TABLE I
TESTS EMPLOYED AND NORMAL VALUES

Reaction	Method Employed		Highest Value in Normal Controls	Clinical Application Described by	
	Authors	Date		Authors	Date
Serum Hexosamine	Elson and Morgan	1933	100 mg. per cent.	Boas and Soffer Kelley Boas and Peterman	1951 1952 1953
Serum Mucoprotein	Winzler and Smyth	1948	4 mg. per cent.	Adams and Dwan Good, Good, Kelley and Glick Kelley, Kerschvink, and Ely Weimer and Redlich Moshin	1950 1950 1952 1953
Total Protein-bound Polysaccharides	Shetlar, modified by Badin, Jackson, and Schubert	1953	100 mg. per cent.	Badin and Glyn Payne, Shetlar, Bullock, Patrick, Hellbaum and Ishmael	1954 1954
Erythrocyte Sedimentation Rate	Westergren	? ? ?	10 mm. females 15 mm. males	Ham and Curtis Lawrence	1938 1953
Plasma Fibrinogen	Cullen and Van Slyke	1920	400 mg. per cent.	Fletcher, Dauphinee, and Ogryzlo Fearnley Fearnley and Bunim	1952 1951 1951
"C"-Reactive Protein	Anderson and McCarty	1950	Normal = 0 Range = 0–4	Bunim, Kuttner, Baldwin, and McEwen Hill Stollerman and others Roantree and Rantz	1952 1951 1953 1955
Serum Resorcidin Turbidity Test	Badin and Choukroun	1950	70 units	Badin and Choukroun	1950

Methods

Initially, the tests were performed twice weekly, but later once weekly estimations were considered to be sufficient. On each occasion when the blood was drawn a full clinical assessment was made.

Subjective Assessment.—This consisted of an overall subjective appraisal by the patient on a scale of 100-0 per cent., the score on the first day of treatment being arbitrarily taken as 100 per cent. in each case.

Objective Assessment.—This was scaled in parallel as follows:

The six most tender, the six most swollen, and the six joints with the most limited movements were selected for serial measurements. Each one was marked out of a total of four points for the characteristics mentioned. Exactly the same method of marking was applied to six appropriate functional tests, and the grip test was also divided into four standards. The total number of points in each group was then added up and expressed as a percentage of the total possible points, assuming the joints to be maximally involved according to our criteria. The resulting figures were then averaged together and scaled up to read 100 per cent. on the first day of treatment.

In this way, all subsequent assessments could be expressed as a percentage of improvement or deterioration as compared with the first day of treatment.

This index is naturally rather a crude one, but it gave consistent results in this series which corresponded with the clinical impression of the patients' progress.

Charts illustrating the correlations between the laboratory tests and the clinical progress were drawn in each of the eight cases. Two of these have been selected for analysis because they illustrate general trends which were constant throughout the group. They also demonstrate certain specific points which seem important.

Fig. 1 (overleaf) concerns a 60-year-old woman with a 2-year history of severe progressive rheumatoid arthritis which had not proved amenable to conventional treatments. Her early response to large doses of hydrocortisone was extremely satisfactory, so that within about 2 weeks she had minimal signs and symptoms.

Corresponding with the clinical suppression there was a very notable fall in the laboratory indices. At this stage there was considerable discussion whether the drug had induced a remission. It is interesting to note, therefore, that, unlike the other indices, the hexosamine, the Winzler mucoprotein, and the total polysaccharides, whilst approaching normal levels, never actually reached them.

However, by the time the dosage had been reduced to 60 mg. per day, there was a slight return of symptoms, but the objective deterioration was

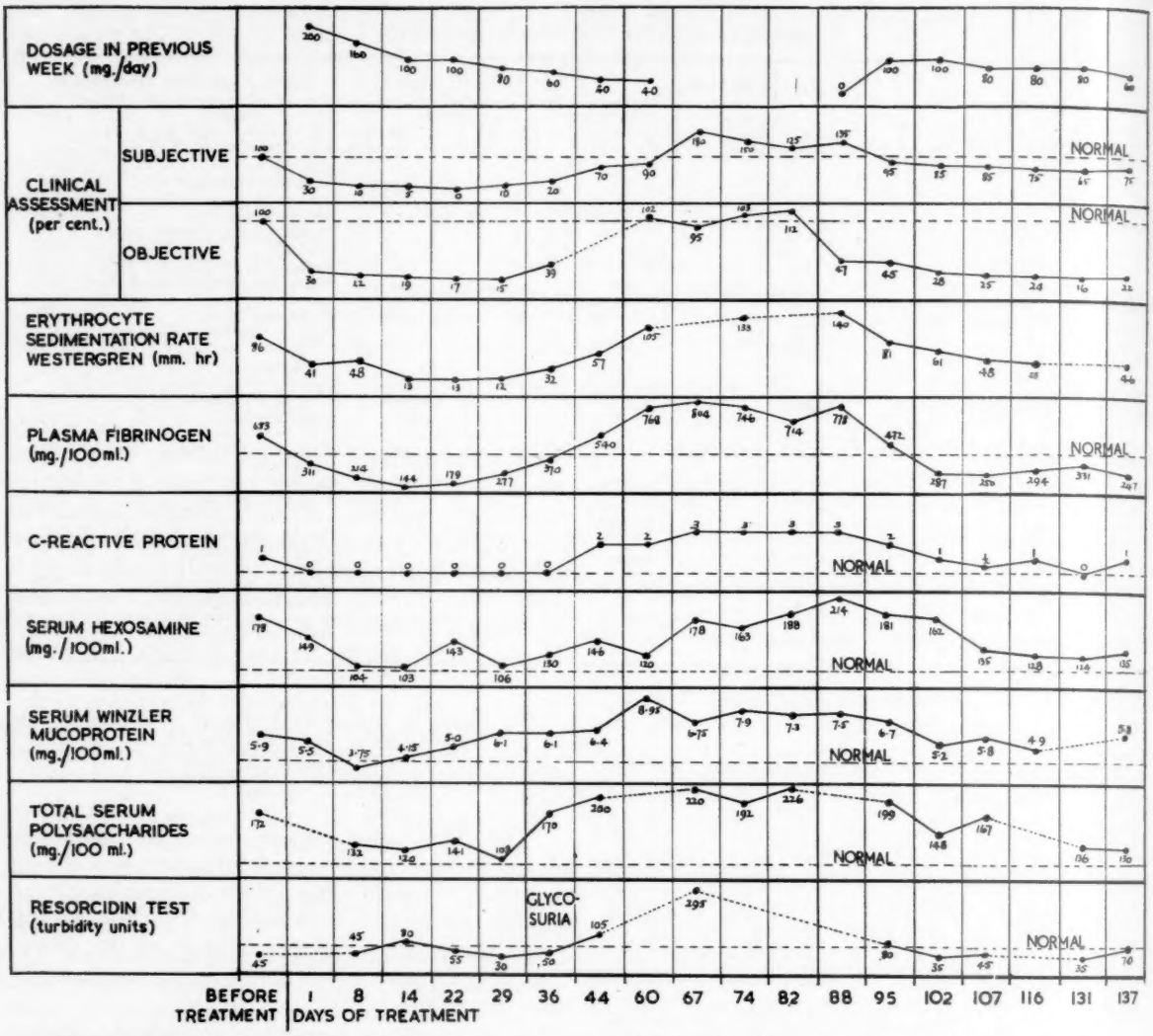


Fig. 1.—Results of tests during hydrocortisone therapy in a woman aged 60 with rheumatoid arthritis of 13 months duration.

minimal, and would normally have escaped notice or been ignored. It is therefore striking that this mild clinical relapse is reflected by a rise in no fewer than five of the laboratory tests, suggesting that the minimal suppressive dose for this phase of the disease had been passed.

Unfortunately, it was not possible to study the effect of raising the dose again at this stage, since almost simultaneously a considerable quantity of sugar was found in her urine on routine testing. The dose was reduced to 40 mg. per day and subsequently withdrawn to enable the carbohydrate metabolism to be fully investigated. The clinical relapse was immediate and devastating, and was more than reflected by the rapid rise in the laboratory indices, in most cases to above their pre-treatment levels.

It was soon apparent that this patient's abject misery, together with the rapid visceral and systemic spread of her disease, would justify a resumption of steroid treatment despite the hazards and problems which are implicit in treating a diabetic with these drugs.

Accordingly hydrocortisone was recommended 5 weeks later with a dosage of 100 mg. per day. On this occasion, there was again a marked objective improvement in the condition of her joints, but the patient insisted that despite this she felt extremely ill and that her muscles were very weak. A muscle biopsy performed at this time, revealed a generalized

panarteritic reaction very similar to that described by Robinson, French, and Duff (1953). It is disturbing to speculate on our responsibility for this development by our rapid fluctuation of dosage.

In view of the marked discrepancy between the arthritic and the systemic response during this second phase of treatment, it is of interest to note again that whilst the "C"-reactive protein and the plasma fibrinogen responded rapidly and returned virtually to normal, the hexosamine, mucoprotein, and polysaccharide levels remained obstinately and significantly raised throughout. The subsequent history was one of inexorable deterioration.

Fig. 2 concerns a 58-year-old woman with a 10-month history of severe rheumatoid arthritis whose response was almost the exact antithesis of that described above. The disease was extremely active at the commencement of treatment, and this clinical assessment was supported by all of the laboratory tests.

The clinical response was rapid and extremely satisfactory. Unlike the other cases in the series, however, she showed no tendency to relapse as the dose was progressively lowered. The treatment with hydrocortisone either precipitated or coincided with a remission in the disease throughout the subsequent period of observation.

It is of particular interest, therefore, that this is also the only case in the series in which the Winzler mucoprotein remained within normal limits for long

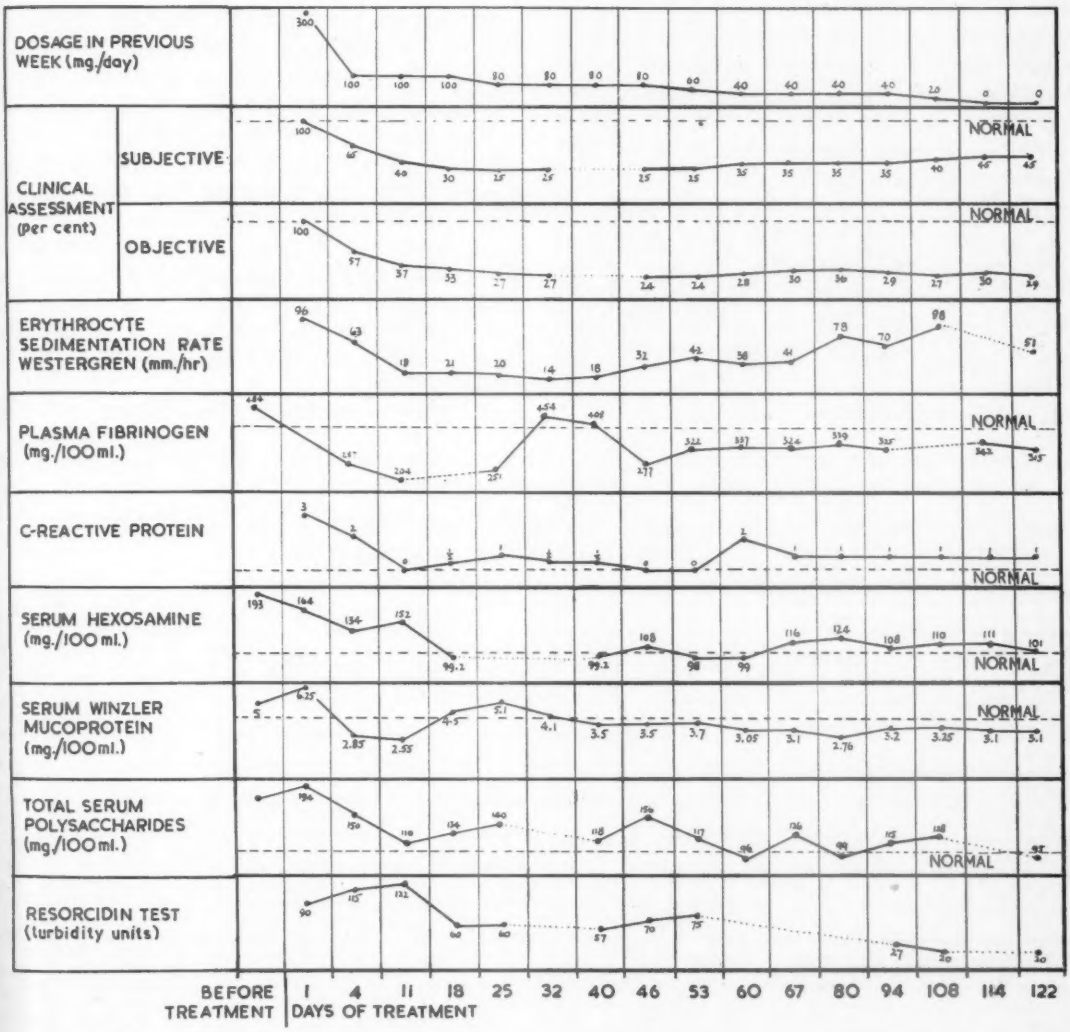

DOSAGE IN PREVIOUS WEEK (mg./day)
CLINICAL ASSESSMENT (per cent)
SUBJECTIVE
OBJECTIVE
NORMAL
ERYTHROCYTE SEDIMENTATION RATE WESTERGREN (mm./hr)
PLASMA FIBRINOGEN (mg./100 ml.)
C-REACTIVE PROTEIN
SERUM HEXOSAMINE (mg./100 ml.)
SERUM WINZLER MUCOPROTEIN (mg./100 ml.)
TOTAL SERUM POLYSACCHARIDES (mg./100 ml.)
RESORCIDIN TEST (turbidity units)
BEFORE TREATMENT
DAYS OF TREATMENT
1 4 11 18 25 32 40 46 53 60 67 80 94 108 114 122

Fig. 2.—Results of tests during hydrocortisone therapy in a woman aged 58 with rheumatoid arthritis of 10 months duration.

periods. The serum hexosamine and the total polysaccharides also remained around normal levels more consistently than in any of the other cases. The other six patients all responded in substantially the same way; Tables II and III illustrate the trends of the *average* levels of mucoprotein 1 and 2 months after the commencement of treatment.

Discussion

Certain conclusions may be drawn from the results obtained in this study:

(1) Active rheumatoid arthritis appears to be consistently associated with abnormally high levels of *all* the indices studied. Furthermore, there seems to be a crude relationship between the clinical measurement of disease activity and the extent to which these levels are raised.

(2) There were extremely few abnormal readings in normal "control" subjects or in patients found to be suffering from insignificant or localized conditions. This observation suggests that it might be possible to adapt these tests for routine "screening" purposes in busy rheumatism clinics.

(3) All the raised indices could be consistently reduced towards normal by adequate treatment with cortisone or hydrocortisone. In most cases, any cessation or reversal of this downward trend was an ominous sign that the dosage had been reduced too far for satisfactory suppression of the symptoms.

(4) It seems significant that, as shown in Tables II and III, the average levels of hexosamine and mucoprotein remain persistently above normal despite a dosage which would be considered excessively high by present-day standards. It is also interesting that the average pre-treatment levels in the eight cases studied were substantially higher than in the unselected group. This was undoubtedly a true reflection of the fact that the patients chosen for study were those with very active and progressively deteriorating arthritis.

Unfortunately, it cannot be claimed that any of the tests were reliable enough in *individual* cases to recommend their routine clinical use. Certainly they could not be trusted as indications of those subtle changes in dose requirements which are vital in the control of problem cases, and to which Hench has given the graphic name "dose tailoring".

It may be, however, that the mucoproteins and hexosamine could be usefully employed in distinguishing between disease remission and the artificial suppression of signs and symptoms.

With regard to their usefulness as "screening tests" for new "anti-rheumatic" drugs, the evidence is also slender but encouraging. For example, one of the patients was treated for 4 days with large daily doses of 150 mg. "Cortisone Stearate" for which the manufacturers were claiming therapeutic potency. This substance appeared to have no clinical effect on the patient, and this was reflected in the complete absence of response in the serological indices.

In striking contrast, another patient in the series

TABLE II

SERUM MUCOPROTEIN LEVELS IN NORMAL CONTROLS AND IN CASES OF RHEUMATOID ARTHRITIS IN DIFFERENT PHASES OF TREATMENT

Serum Mucoprotein Level (mg./100 ml.)	Normals	Untreated Unselected Rheumatoid Arthritics	Selected Series of Severe Rheumatoid Arthritics Treated with Cortisone or Hydrocortisone		
			Before Treatment	After 1 month of Treatment	After 2 months of Treatment
2–2·9	5	4	—	—	—
3–3·9	8	9	—	—	1
4–4·9	5	7	—	2	3
5–5·9	—	8	2	4	1
6–6·9	—	8	2	1	3
7–7·9	—	1	3	1	—
8–8·9	—	2	—	—	—
9–9·9	—	1	1	—	—
Total	18	40	8	8	8
Average	3·5	5·1	7·0	5·7	5·25

was treated for 3 days with daily doses of 80 mg. "Cortisone Aldehyde" before being transferred to the conventional hydrocortisone free alcohol. His clinical response, though not dramatic, was easily measurable, and six of the seven laboratory indices showed a parallel fall.

Perhaps the most striking result of this study has been the sharp contrast between the lability of tests such as the erythrocyte sedimentation rate, "C"-reactive protein, fibrinogen, and resorcidin, and the obstinacy of indices such as the serum hexosamine, Winzler mucoprotein, and total protein-bound polysaccharides. The latter group of tests was not affected by evanescent fluctuations in the disease activity and, as already indicated, seldom reached normal levels in our patients.

It is tempting to argue from this observation that, although all the tests are non-specific in the sense that they can be affected by many different diseases, there is a suggestion of a fundamental distinction between them. This may be related to the fact that in the second group we are measuring the serological analogues of the intercellular ground substance.

We know that in the rheumatic diseases there is a profound alteration in this connective tissue and, although this is not clearly defined, it has been suggested that it takes the form of a depolymerization of the mucopolysaccharides which constitute the ground substance. There is further experimental evidence (Pirani and Catchpole, 1951) that, when these glycoproteins are depolymerized (as for example in scurvy), they become more water-soluble, and that this is reflected in a rise in their serum concentration. Finally, it is well established that one of the actions of cortisone and its analogues is to antagonize the depolymerizing action of hyaluronidase on hyaluronic acid, which is one of the essential constituents of the ground substance (Winter and Flataker, 1950).

These facts can be welded into a plausible hypothesis suggesting that the measurement of the concentration of circulating serum glycoproteins does provide a logical index of underlying disease activity in patients suffering from rheumatoid arthritis. In addition, the influence exerted upon them by the steroid drugs may well be a true reflection of their "anti-rheumatic" action. Further investigation of this hypothesis seems justified.

None of these tests measure a pure chemical substance, therefore it is of interest to determine the degree to which their levels are correlated. The coefficient of correlation between the Winzler mucoproteins and the total protein-bound polysaccharides was only 0·62. To some extent this relatively low figure can be explained on a purely technical basis. It has been discussed in greater detail in a previous communication (Badin and Glyn, 1954), and the conclusion reached was that the correlation was better at the commencement of treatment and that most of the discrepancies occurred in the falling portions of the curve. From this it was inferred that the synthesis of these two

TABLE III

SERUM HEXOSAMINE LEVELS IN NORMAL CONTROLS AND IN CASES OF RHEUMATOID ARTHRITIS IN DIFFERENT PHASES OF TREATMENT

Serum Hexosamine Levels (mg./100 ml.)	Normals	Untreated Unselected Rheumatoid Arthritics	Selected Series of Severe Rheumatoid Arthritics Treated with Cortisone or Hydrocortisone		
			Before Treatment	After 1 month of Treatment	After 2 months of Treatment
80– 89	3	2	—	—	—
90– 99	8	2	—	2	—
100–109	5	2	—	—	1
110–119	1	2	—	1	—
120–129	—	6	—	1	—
130–139	—	8	—	2	2
140–149	—	—	1	1	3
150–159	—	3	1	1	1
160–169	—	3	2	—	1
170–179	—	1	4	—	—
Total	17	30	8	8	8
Average	98	122	166	125	141

substances was probably under common control but that their catabolism took place along different pathways.

With regard to the mucoproteins and the hexosamine, the high degree of correlation is shown in Fig. 3 which refers to patients who were under treatment at the time of study. Exactly the same picture, however, was demonstrated in patients not undergoing any form of therapy.

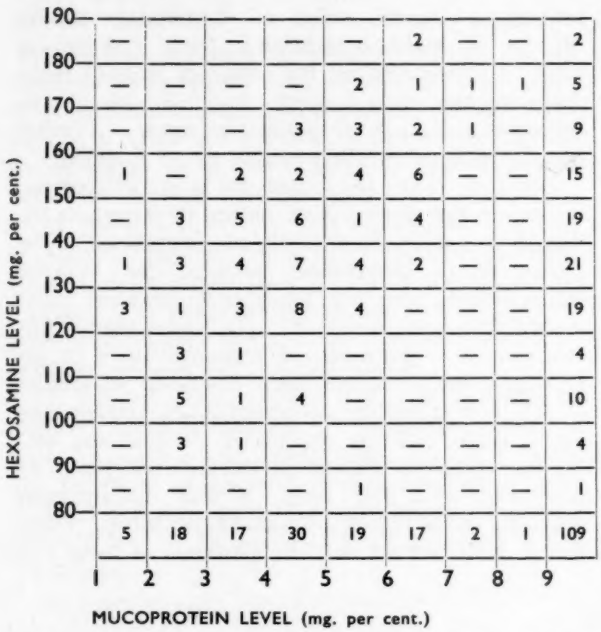


Fig. 3.—Mucoprotein and hexosamine levels in 109 patients with rheumatoid arthritis treated with cortisone.

To a limited extent the correlation can be explained by the finding of Winzler, Devor, Mehl, and Smyth (1948), and Winzler and Smyth (1948) that his mucoprotein fraction contained 11·9 per cent. of hexosamine, but on the basis of his figures it can be calculated that this source of hexosamine cannot account for more than about 10 to 12 per cent. of the total amount present. This is certainly not sufficient to explain the degree of correlation which has been demonstrated. There is, therefore, a strong suggestion of a common source of origin for these two substances, or at least certain common factors controlling their blood levels.

Summary

An attempt has been made to apply a battery of "acute phase" serological estimations to the problems of controlling long-term steroid therapy in rheumatoid arthritis. The results were disappointing from the point of view of their application to individual cases, but several interesting features emerged about the interpretation of these tests and their possible relationship to one another, and to the underlying disease process. These are discussed in some detail.

A numerical method of recording and comparing subjective and objective clinical fluctuation in rheumatoid arthritis is described. It gives consistent results, at least in short-term therapeutic trials.

The material which forms the basis of this paper was obtained during the tenure of a Masonic Fellowship on the Study Group on Rheumatic Diseases, New York University, Bellevue Medical Centre. The author wishes to record his sincere gratitude for the advice and encouragement he has received from many colleagues and specifically from Drs. Currier McEwen and Morris Ziff who sponsored the project.

REFERENCES

Adams, F. H., and Dwan, P. F. (1950). *J. Lancet*, **70**, 389.
Anderson, H. C., and McCarty, M. (1950). *Amer. J. Med.*, **8**, 445.
Badin, J., and Choukroun, J. (1950). *Sem. hôp. Paris*, **26**, 1223 and 1243.
—— and Glyn, J. (1954). *Proc. soc. exp. Biol. (N.Y.)*, **86**, 150.
——, Jackson, C., and Schubert, M. (1953). *Ibid.*, **84**, 288.
Bagnall, A. W. (1951). *Canad. med. Ass. J.*, **65**, 125.
Boas, N. F., and Peterman, A. F. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **82**, 19.
——— and Soffer, L. J. (1951). *J. clin. Endocr.*, **11**, 39.
Bunim, J., Kuttner, A. G., Baldwin, J. S., and McEwen, C. (1952). *J. Amer. med. Ass.*, **150**, 1273.
Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M. (1952). *Brit. med. J.*, **1**, 397.
Cullen, G. E., and Van Slyke, D. D. (1920). *J. biol. Chem.*, **41**, 587.
Elson, L. A., and Morgan, W. T. J. (1933). *Biochem. J.*, **27**, 1824.
Fearnley, G. R. (1951). *Lancet*, **2**, 501.
——— and Bunim, J. J. (1951). *Ibid.*, **2**, 1113.
Fletcher, A. A., Dauphinee, J. J., and Ogryzlo, M. A. (1952). *J. clin. Invest.*, **31**, 561.
Good, R. A., Good, T. A., Kelley, V. C., and Glick, D. (1950). *Fed. Proc.*, **9**, 178.
Ham, T. H., and Curtis, F. C. (1938). *Medicine*, **17**, 447.
Hill, A. G. S. (1951). *Lancet*, **2**, 807.
Kelley, V. C. (1952). *J. Pediat.*, **40**, 413.
——, Kirschvink, J. F., and Ely, R. S. (1952). *Amer. J. Physiol.*, **171**, 738.
Lawrence, J. S. (1953). *Annals of the Rheumatic Diseases*, 12, 206.
Payne, R. W., Shetlar, M. R., Bullock, J. A., Patrick, D. R., Hellbaum, A. A., and Ishmael, W. K. (1954). *Ann. intern. Med.*, **41**, 775.
Pirani, C. L., and Catchpole, H. R. (1951). *A.M.A. Arch. Path.*, **51**, 597.
Ragan, C., Demartini, F., Lamont-Havers, R., Jessar, R. A., Vaillancourt, D., and Grokoest, A. W. (1952). *Bull. N.Y. Acad. Med.*, **28**, 493.
Roantree, R. J., and Rantz, L. A. (1955). *A.M.A. Arch. intern. Med.*, **96**, 674.
Robinson, W. D., French, A. J., and Duff, T. I. (1953). *Annals of the Rheumatic Diseases*, **12**, 323.
Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H. (1953). *Amer. J. Med.*, **15**, 645.
Vaughan, J. H., Bayles, T. B., and Favour, C. B. (1951). *Proc. soc. exp. biol. (N.Y.)*, **76**, 274.
Weimer, H. F., and Redlich-Moshin, J. (1953). *Ibid.*, **84**, 34.
Winter, C. A., and Flataker, L. (1950). *Fed. Proc.*, **9**, 137.
Winzler, R. J., Devor, A. W., Mehl, J. W., and Smyth, I. M. (1948). *J. clin. Invest.*, **27**, 609.
—— and Smyth, I. M. 1948). *Ibid.*, **27** 617.

Aide du laboratoire a la thérapie stéroide

RÉSUMÉ

Un certain nombre d'anomalies sérologiques non-spécifiques associées à des processus inflammatoires ou nécrotiques a été décrit et nommé "réactions de la phase aiguë". On a essayé d'appliquer une série de telles réactions aux problèmes de contrôle de la thérapie stéroïde à long terme, dans l'arthrite rhumatismale. Les resultats furent décevant au point de vue de leur application à des cas individuels, mais plusieurs caractères intéressants se révélèrent, relatifs à l'interprétation de ces réactions, à leur rapport entre elles et avec le processus morbide. Ces caractères sont discutés avec quelques détails.

Une méthode numérique d'enregistrement et de comparaison des fluctuations cliniques subjectives et objectives dans l'arthrite rhumatismale est décrite. Elle donne des résultats valables, au moins en ce qui concerne les essais thérapeutiques à court terme.

Contribución del laboratorio a la terapia esteroide

SUMARIO

Un cierto número de anomalías serológicas no específicas, asociadas a procesos inflamatorios o necróticos fué descrito y nombrado "reacciones de la fase aguda". Una serie de tales reacciones fué aplicada a problemas de control de la terapia esteroide de plazo largo en la artritis reumatoide. En su aplicación a casos individuales, los resultados fueron mediocres, pero se hicieron observaciones interesantes respecto a la interpretación de estas reacciones, las relaciones entre ellas y con el proceso mórbido. Estas observaciones se discuten detalladamente.

Se describe un método numérico para notar y comparar las fluctuaciones clínicas subjetivas y objetivas en la artritis reumatoide. Este método ofrece resultados válidos, a lo menos en los ensayos terapéuticos de plazo corto.

Ann. rheum. Dis. (1956), **15**, 346.

A HAND CORSET

BY

H. HERSCHEL

Amsterdam

(RECEIVED FOR PUBLICATION OCTOBER 5, 1956

The problem of finding a suitable splint or prosthesis for the arthritic hand has lost nothing of its actuality. For this reason I have concentrated my attention upon improving the splints now generally in use, and have designed a support, to which I should like to give the name of "hand corset". In this I do not claim any originality, as I have made ample use of the work of others.

The hand corset consists of an ordinary glove of soft material, the fingers of which are supported by long springs of flexible coiled steel wire. These adjustable springs are inserted into special slits and cut to the required length. Figs 1 and 2 make the "construction" of the splint quite clear, and obviate a more elaborate description. This glove admits of an elastic fixation of the hand, fingers, and wrist, without putting any additional strain on the joints. If any of the springs cause pressure on a particular joint, the trouble can be adjusted by a simple bending of the flexible "stay".

This hand corset has the following advantages among others:

(*a*) it has an attractive appearance, which is undoubtedly of psychological value;
(*b*) every glove can be made to measure, so as to fit any hand, however deformed;
(*c*) it allows elastic fixation in the right position;
(*d*) the strength of the springs may be altered at will, by using stronger or weaker springs, or by inserting one or more extra springs.

I usually adjust the springs in the position of function of the hand. Whether contracture positions can be prevented in this way is uncertain. Even if one succeeds in correcting the dorsoflexion contraction, that crippling malformation of the

Fig. 1.—The hand corset in use.

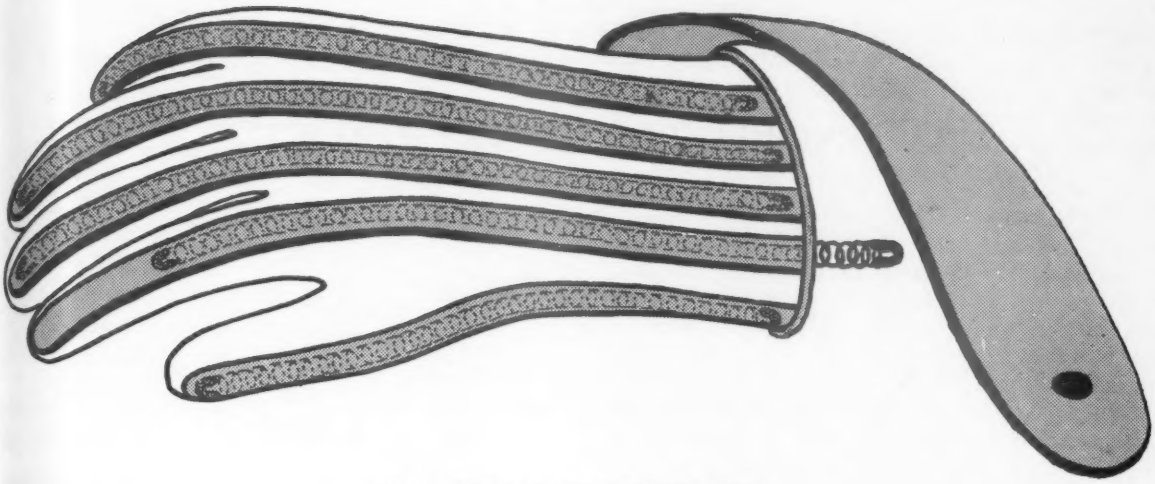


Fig. 2.—Diagram to show insertion of springs.

middle joints of the digits, it is not certain whether this correction will prove permanent.

In fitting the hand corset special care should be taken that the springs do not press on swollen or painful joints, this is made easy by the fact that the springs may be bent in all directions. For practical purposes it may be advisable to cut away the material of the fingertips, so that the glove becomes a kind of mitten, permitting the patient to use the hand with the sense of touch unimpaired.

The author wishes to acknowledge his debt to Dr. G. Van Dam and Mrs. A. Bollen-Kuylaars of Amsterdam.

Gant prothétique

RÉSUMÉ

On décrit un gant prothétique pour la main arthritique. Il s'agit d'un gant ordinaire en toile souple dont les doigts son renforcés par des ressorts à boudin en fil d'acier, facilement ajustables. Ce gant permet le maintien souple de la main, des doigts et du poignet sans imposer une fatigue supplémentaire aux articulations.

Guante protético

SUMARIO

Se describe un guante protético para la mano artrítica. Se trata de un guante ordinario de tela flexible con dedos reforzados por resortes de acero, facilmente ajustables. Este guante permite el mantenimiento flexible de la mano, de los dedos y de la muñeca sin cansancio adicional de las articulaciones.

Ann. rheum. Dis. (1956), **15**, 348.

PSORIASIS AND ARTHRITIS

BY

V. WRIGHT

Leeds

(RECEIVED FOR PUBLICATION JULY 23, 1956)

The literature on this subject shows considerable divergence of opinion on the significance of the association of psoriasis and erosive arthritis, and on what may be said to comprise "psoriatic arthropathy", if the term is to be used at all. The difficulties of the problem are increased by the fact that according to the predominant complaint the patient may fall into the hands of either the rheumatologist or the dermatologist, and escape the statistical eye of one or the other. The difficulty in assessing the incidence is indicated by the diverse figures given in the literature—an aspect recently reviewed by Gribble (1955). Among dermatologists, however, it is generally agreed that atrophic arthritis is commoner among patients with psoriasis (Leczinsky, 1948: 5·8 per cent. males, 7·9 per cent. females; Ingram, 1954: 7 per cent.) than among the general population. Among rheumatologists it is agreed by the majority that psoriasis occurs in about 3 per cent. of patients with atrophic arthritis (Dawson and Tyson, 1937; Bauer, 1939) as compared with 0·7 per cent. in the general population (Ingram, 1954), while there is no significant increase in the incidence among patients with osteo-arthritis.

Many workers have endeavoured to define an entity "psoriatic arthropathy", and the following definitions have been suggested:

(1) A form of atrophic arthritis associated with psoriasis and exhibiting a reasonable degree of synchronous activity as evidenced by remissions and relapses in arthritis and cutaneous manifestations (Lane and Crawford, 1937; Jeghers and Robinson, 1937; Epstein, 1939).

(2) Arthritis restricted to the distal interphalangeal joints associated with psoriasis (Bauer, Bennett, and Zeller, 1941).

(3) A syndrome in which both skin lesions and arthritic manifestations are atypical (Dawson, 1937), or in which the joints are improved by treatment of the skin (O'Leary, 1943).

(4) A peculiarly destructive form of arthritis associated with psoriasis (Fawcitt, 1950).

Other authors feel there is no justification for the use of the term, because they think the two conditions are coincidental. The problems therefore are:

(1) Is there an entity "psoriatic arthropathy"?
(2) If there is, what are its characteristics?

Most of the published reports have dealt with cases fulfilling one or other of the diagnostic criteria above, and there have been few broad surveys of the general field of concomitant psoriasis and joint disease. The present study was undertaken in the light of the striking absence of the Waaler-Rose phenomenon in all cases of erosive arthritis associated with psoriasis seen before the start of the survey, and an attempt has been made to answer the problems by contrasting three groups of patients, one with psoriasis and arthritis, one with uncomplicated rheumatoid arthritis and one with uncomplicated psoriasis.

Material and Methods

In all, 42 patients with psoriasis and arthritis have been considered, 34 with erosive arthritis (the term "erosive arthritis" being used in preference to "rheumatoid arthritis" so that the issue may not be prejudged), six with degenerative joint disease, one with gout, and one with rheumatic fever. In all cases the diagnosis of psoriasis was confirmed by a dermatologist (Dr. D. S. Wilkinson). In five, information was incomplete, two patients having died, the other three having left the district. The others were examined personally, their serum was submitted to certain laboratory tests, and radiographic studies were made. This group has been contrasted with 55 unselected patients with rheumatoid arthritis who were found to have a positive Differential Agglutination Test (Waaler-Rose), and with an unselected group of patients with psoriasis but no joint manifestations (310 patients in all).

Findings

I. Erosive Arthritis

Sex Incidence.—It is of interest that of the 34 patients, eighteen were men and sixteen were women. While this series is too small to be of statistical significance, the point is of obvious importance, since both rheumatoid arthritis and psoriasis, occurring singly, were found to be commoner in women (Table I).

TABLE I
SEX INCIDENCE

	Series	A	B	C
	No. of Patients	34	55	310
	Diagnosis ..	Psoriasis and Erosive Arthritis	Rheumatoid Arthritis	Psoriasis
Sex (per cent.)	Female ..	47	75	59
	Male	53	25	41

The increased proportion of males among patients with psoriasis and erosive arthritis has been noted before by French writers (Darier, 1920; Darier, Civatte, and Tzanck, 1947), and Vilanova and Piñol (1951), in reviewing the literature, observed a similar incidence to the present figures (82 males to 68 females; 54·7 to 45·3 per cent.).

Onset of Psoriasis.—In terms of site of origin or age at onset the skin lesions differed little from uncomplicated psoriasis, except that in the cases with arthritis there was a tendency towards a later age at onset. In 16 per cent. of patients the nails were affected initially.

Onset of Skin and Nail Lesions related to Onset of Arthritis.—Fig. 1 shows that psoriasis usually preceded the onset of arthritis in these patients, developing first in 64 per cent. and preceding the arthritis by anything from 37 years to 2 months. In 13 per cent. the psoriasis and arthritis were synchronous in onset, and in 23 per cent. the skin lesions came second. It is tempting to suggest that some cases of erosive arthritis with a negative differential agglutination test (D.A.T.) are destined to develop psoriasis. The only clue to this may be the family history, for 35 per cent. of the patients with psoriasis and erosive arthritis had a family history of psoriasis as compared with 2 per cent. of the rheumatoid group (Fig. 2).

In some ways joint changes seemed more closely related to lesions of the nails than to psoriasis of the skin. Only 13 per cent. had no nail changes. In cases of psoriasis as a whole (including some with arthritis) the nails are involved in between 10 and 25 per cent. of patients, the figure of 15 per cent.

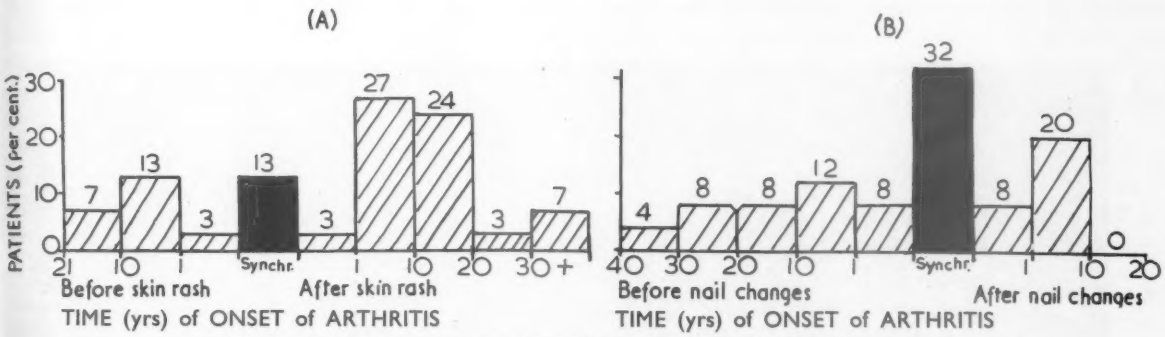


Fig. 1.—Interval between onset of arthritis and (A) skin rash, (B) nail changes.

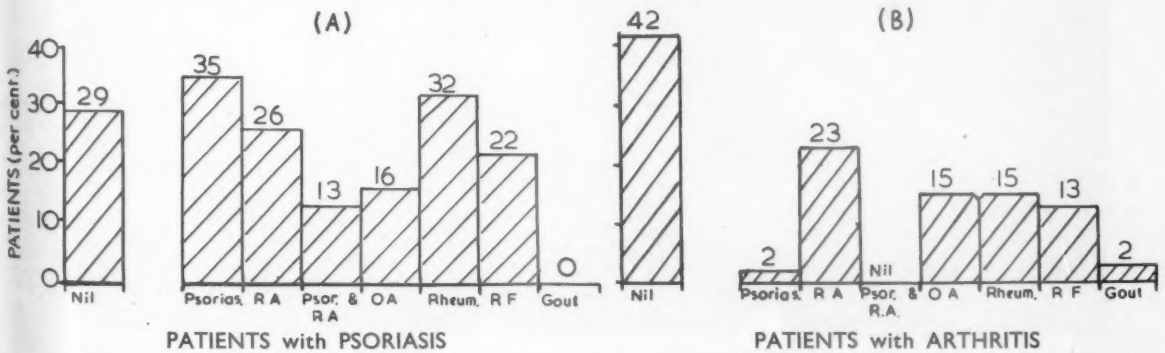


Fig. 2.—Family history of psoriasis and rheumatic diseases: (A) in patients with psoriasis; (B) in patients with rheumatoid arthritis.

given by Pardo-Castello (1936) being about the average in the literature. Widely varying figures are however quoted: Crawford (1938) gives an incidence as high as 49·8 per cent. and the next highest figure is 25 per cent. Among the group of patients with uncomplicated psoriasis, 18 per cent. had changes of the finger nails (23 per cent. men, 14·7 per cent. women). Only two patients with psoriasis and erosive arthritis never had nail changes, and two more had lesions of the nails but not of the skin. In relation to the arthritis, nail changes came first in 28 per cent., with a lapse of 4 months to 10 years, and arthritis came first in 40 per cent., with an intervening period of 6 months to 35 years (Fig. 1). Although skin changes and arthritis came on simultaneously in only 13 per cent., nail changes were synchronous with arthritis in 32 per cent. The onset of the various manifestations was closely related (*i.e.* one occurred within 12 months of the other) in 19 per cent. between joint and skin changes, and 48 per cent. between joint and nail changes. Moreover, exacerbations were more often synchronous in nails and joints than in skin and joints.

Thus in 53 per cent. nail and joint changes either developed simultaneously, or were subject to synchronous exacerbation. Only 24 per cent. had a similar relationship between the skin and joints, an equal number claimed an inverse relationship, and in 52 per cent. there was no relation at all.

A topographical association between nail and joint changes was sometimes evident (Fig. 3), but a similar association with the site of skin lesions could not be demonstrated.

Onset of Arthritis.—The average age at onset of arthritis in the two groups (Table II) is compared with the results obtained in the Empire Rheumatism Council Survey (1950).

TABLE II

AVERAGE AGE AT ONSET, BY SEX

Age (yrs)	Sex		
	Male	Female	Total
Psoriasis with Erosive Arthritis ..	37	33	35
Uncomplicated Rheumatoid Arthritis	41	43	42
E.R.C. Survey (Rheumatoid Arthritis)	42	41	41·5

Contrasted by decades (Fig. 4, opposite), there is a marked similarity in the age at onset, apart from a higher incidence in the second decade among those with psoriasis.

There was no significant difference in the percentage of those with an acute onset (Table III, opposite), nor was there any difference in the numbers with a history of pyrexia at the onset of the arthritis.

Fig. 3.—Topographical association of distal interphalangeal joint and nail lesions in erosive arthritis with psoriasis. The index and middle fingers of the left hand show a contrast between affected and unaffected nails.

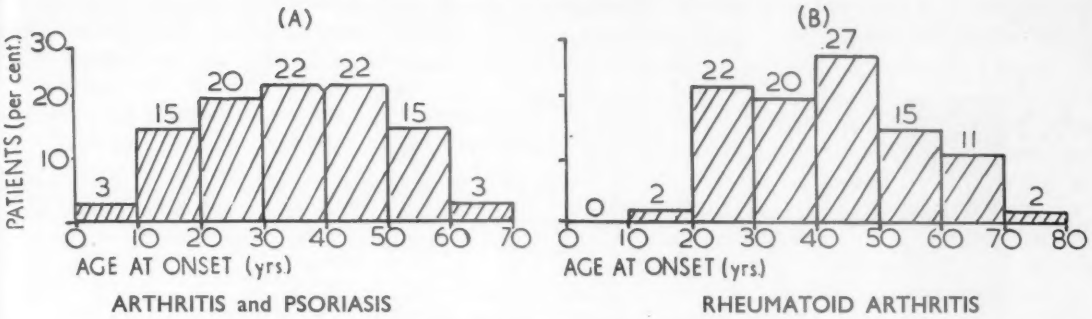


Fig. 4.—Age at onset: (A) of patients with arthritis and psoriasis; (B) of patients with rheumatoid arthritis.

TABLE III
ACUTE ONSET OF ARTHRITIS, BY SEX
(Per cent.)

Sex	Male	Female	Total
Psoriasis and Erosive Arthritis	29	40	34
Uncomplicated Rheumatoid Arthritis	36	29	32

TABLE IV
NON-POLYARTICULAR DISEASE AT ONSET, BY SEX

Sex	Male	Female	Total
Psoriasis with Erosive Arthritis	82	60	72
Uncomplicated Rheumatoid Arthritis	54	43	45

Sherman (1952), in her review of psoriasis with arthritis, comments that the onset is not polyarticular, whereas Jeghers and Robinson (1937) maintain that this is so, but it should be noted that their diagnostic criteria differs. In the present series 31 per cent. of cases were polyarticular at onset and 69 per cent. were not. Among patients with rheumatoid arthritis 41 per cent. are monarticular at the start according to the Empire Rheumatism Council Survey; the proportion was similar in this smaller group of rheumatoid patients. A polyarticular onset is therefore less common in the psoriatic group (Table IV).

The joints involved initially are shown in Fig. 5. The distal interphalangeal joints were the most frequent targets for the initial attack in patients with psoriasis and erosive arthritis. Otherwise the site of onset is virtually the same in both groups.

Course of Arthritis.—From the history two impressions emerged:

(1) That a patient could have severe affection of the joints and then apparently recover completely. Such complete remissions occurred in 50 per cent. One woman, virtually confined to bed for 2 years, recovered and remained fit for the next 8 years with no active joint trouble or residual disability.

(2) The major part played by stiffness in the symptomatology—68 per cent. emphasized this in their history and in 26 per cent. of the total it was the predominant complaint.

From the history the joints involved are virtually the same as in rheumatoid arthritis, apart from a predilection for the distal interphalangeal joints.

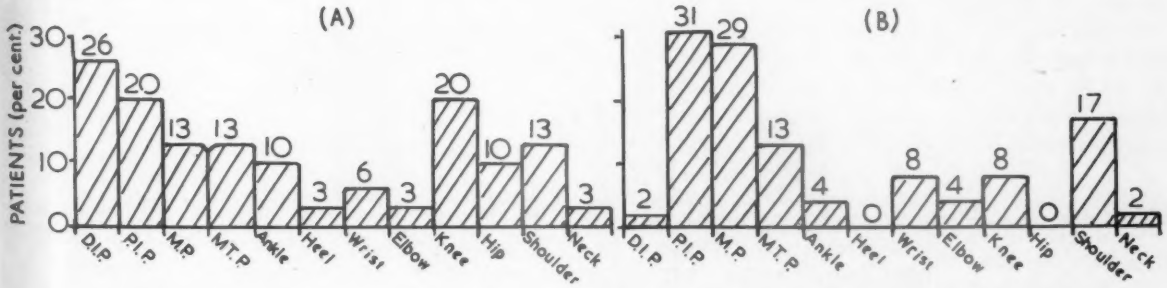


Fig. 5.—Joints involved initially: (A) in patients with arthritis and psoriasis; (B) in patients with rheumatoid arthritis.

These last joints, if involved, are usually affected at the onset of the arthritis (Fig. 6).

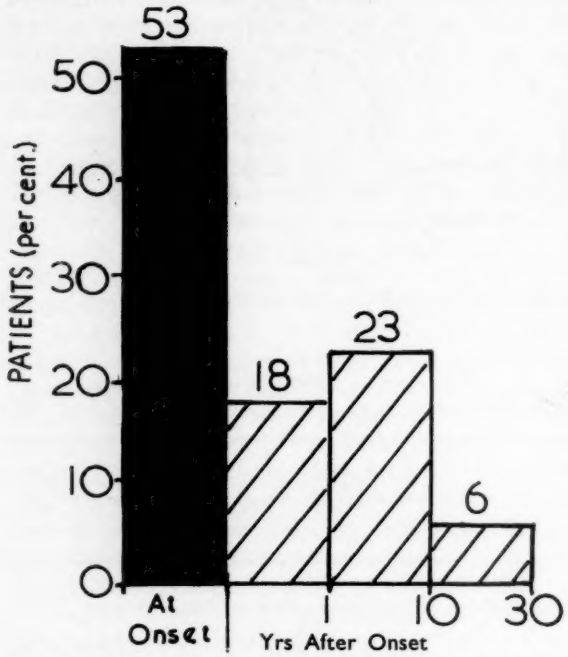


Fig. 6.—Interval between involvement of distal interphalangeal joints and onset of arthritis elsewhere.

Furthermore, graphs relating their involvement to the onset of skin and nail changes show that once again there is closer relationship between the joints and the nails than between the joints and the skin in synchronicity of onset (Fig. 7).

Sherman (1952) states that the clinical appearance of the joints may simulate gout, and specific inquiry was accordingly made on this point. In 39 per cent. such a diagnosis had been made at some time.

As far as disability is concerned, judging from the time lost from work through the patient's arthritis, the disease seems to be either severe and crippling, or very mild. Mild cases were commoner than severe ones. Cases of intermediate severity were, however encountered.

Skin and Nail Lesions.—These were typical in distribution. The palms and soles were affected in only 9 per cent. in contrast to many reports giving a higher incidence (Cannon, 1934; Wassmann, 1949). The psoriasis was extensive in only three patients; two of these were completely bedridden with arthritis and the third was severely disabled.

In 81 per cent. changes were present in the nails. In two patients the nails only were involved, an uncommon but recognized phenomenon (White, 1938; MacKenna, 1950). The order of frequency of changes in the nails was:

(1) Thickening, beginning in the distal part.
(2) Separation from the subungual bed.
(3) Ridging and cracking.
(4) Pitting.
(5) Spoon shape, secondary to hyperkeratosis.

These results disagree with those of some other investigators (Vilanova and Piñol, 1951), who have described pitting as the most common symptom. Pitting may well be the most characteristic feature, although it is occasionally seen in chronic eczema, exfoliative dermatitis, and other inflammatory skin diseases (Pardo-Castello, 1936).

Joints.—Although the arthritic process showed a predilection for the distal interphalangeal joints, in no case was the joint involvement confined to them, and even in a "classical" case where three such joints of each hand were involved with the corresponding nails, one metacarpo-phalangeal and one

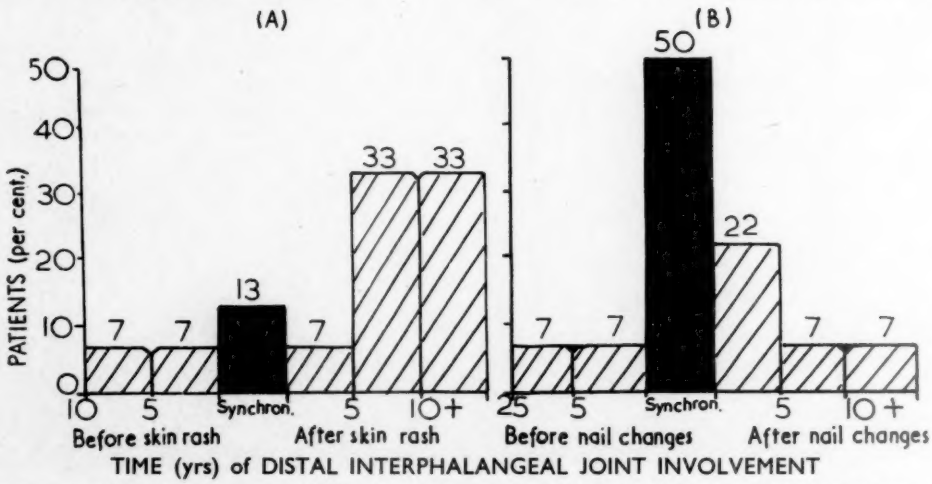


Fig. 7.—Interval between involvement of distal interphalangeal joints and onset of (A) skin rash, (B) nail changes.

proximal interphalangeal joint were also involved. There would therefore seem to be no rational basis for designating patients with distal interphalangeal joint involvement only as suffering from "psoriatic arthropathy", and for excluding patients with more joints involved. When the distal joints of the fingers were involved, the change seemed to affect the whole finger tips, producing spade-like ends with considerable swelling over the joint.

Three patients showed a clinical picture of ankylosing spondylitis with peripheral joint involvement. This high incidence is in accord with recent reports (Sherman, 1952; Sterne and Schneider, 1953; Fletcher and Rose, 1955).

In an attempt to assess the severity of the arthritis special note was made of the state of the joints first involved, and of the presence of ulnar deviation. The latter was present in 36 per cent. of the rheumatoid group as compared with 13 per cent. of those with psoriasis and erosive arthritis. Four broad stages were distinguished in the current state of the joints initially affected:

(1) No abnormality;
(2) Mild stigmata, including slight limitation of movement, swelling without much tenderness, slight pain on movement, crepitus, and slight deformity without ankylosis or subluxation;
(3) Recent exacerbation;
(4) Severe involvement, including gross deformity, ankylosis, or subluxation.

Table V shows the relative frequency of these divisions. There is a slight tendency for more of the rheumatoid group to show stigmata in the joints initially affected. This is of interest since the arthritis was of shorter duration than in the psoriatic group. Its significance may be lessened by the fact that the patients with rheumatoid arthritis all sought help because of the condition of their joints, while many of those with psoriasis and erosive arthritis had presented on account of their skin manifestations.

Associated Findings.—Only one arthritic patient of those with psoriasis had subcutaneous nodules and effusions in the extensor tendon sheaths. He had a positive Differential Agglutination Test (D.A.T.). This is of interest since subcutaneous nodules are regarded by many as the most characteristic lesion of rheumatoid arthritis (Bauer, 1939; Bennett, 1943). Among the group of patients with rheumatoid arthritis, 17 per cent. had subcutaneous nodules on examination, and 22 per cent. gave a history of nodules at some time during the course of the arthritis.

TABLE V

STATE OF JOINTS INITIALLY AFFECTED

(Per cent. of patients)

Grade of Involvement ..	1	2	3	4
Psoriasis and Arthritis ..	39	35	13	13
Rheumatoid Arthritis ..	22	45	13	20

The complete absence of subcutaneous nodules among patients with psoriasis and erosive arthritis with a negative D.A.T., strikingly differentiates these patients from those with uncomplicated rheumatoid arthritis.

Laboratory Investigations.—The haemoglobin, E.S.R. (Wintrobe), and white cell counts were estimated in the patients with psoriasis and erosive arthritis. No laboratory investigations were done on those with uncomplicated psoriasis, but comparison has been made with results obtained at first attendance from an unselected group of 69 patients with rheumatoid arthritis and a positive D.A.T. The results are not strictly comparable since the patients with psoriasis were sought, whereas those with rheumatoid arthritis attended a rheumatology clinic of their own volition. Under these circumstances the psoriatic group showed less anaemia, a lower E.S.R., and more normal white cell counts.

C-reactive protein was found in the sera of 43 per cent. of the patients with psoriasis and erosive arthritis.

The D.A.T. was positive in only two patients with psoriasis and erosive arthritis (*i.e.* 94 per cent. negative). The method used was a modification of the techniques of Rose, Ragan, Pearce, and Lipman (1948) and Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks (1955). Sera producing agglutination of sensitized sheep red cells in a dilution of 1:16 or higher were taken to be positive, providing the heterophile antibody was present in minimal quantity or had been absorbed previously. It is interesting that the one patient in the series with nodules and tendon sheath effusions should be one of those with a positive D.A.T. and that in addition he should be one of the two without nail changes. It seems possible that in these patients the occurrence of psoriasis and rheumatoid arthritis was a true coincidence, while in the others the skin and joint features were manifestations of a single disease process.

In patients with erosive arthritis and a negative D.A.T., the history and clinical examination should be carefully searched for psoriasis. In fact the diagnosis of one of this series came to light in such a manner.

The results of other laboratory investigations are given in Table VI.

The serum cholesterol level was estimated by a modification of Sackett's method (King, 1951). The normal range is 140–215 mg. per 100 ml. The level was raised in 28 per cent. of the group with psoriasis and erosive arthritis, the values in three patients being over 300 mg. per 100 ml. High values are said to occur in psoriasis alone (Epstein, 1939), although this is not universally agreed (Tobias, 1939).

Because many authors regard gross bone destruction as a feature of psoriatic arthropathy, the serum alkaline phosphatase activity was measured in King Armstrong Units, 12 K.A. units being considered the upper limit of normal. In both groups the majority had a raised value; the highest (72 K.A. units) was in a severely crippled psoriatic patient. The increase of serum alkaline phosphatase activity was most closely related to the number of joints involved and to the duration of the arthritis in both groups. There was no evidence of Paget's disease in any of these patients.

The few references in the literature to the level of the serum proteins in psoriasis and erosive arthritis state that they are normal (Shlionsky and Blake, 1936; Sherman, 1952). In the present series the levels were estimated by the method of Martin and Morris (1949), normal values in our laboratory being:

Serum globulin 1·7–3·8 g. per 100 ml., serum albumin 3·0–4·3 g. per 100 ml.

High globulin values were obtained in 17 per cent. of the psoriatic group and in 22 per cent. of the rheumatoid group. The findings were confirmed by Kunkel's zinc sulphate test (1947) and qualitative electrophoresis. The most common finding with the latter method was an increase in the γ-globulin and β-globulin bands which merged into each other.

Treatment.—Many reports have recorded that the joint symptoms subside with treatment of the psoriasis (Gross, 1928; Jeghers and Robinson, 1937; Epstein, 1939; Franks and Wallace, 1942; O'Leary, 1943), but experience in the present series is sharply at variance with this finding. In fact only one patient had experienced this regression, and it was probably significant that he had been at rest in hospital at the time.

The arthritis responded to the usual methods of salicylate therapy, physiotherapy, cortisone, corticotrophin, and prednisolone in selected cases, local hydrocortisone, and gold. Ragan and Tyson (1946) found a large proportion of toxic reactions in psoriatic patients receiving gold. In none of eleven patients in this series to whom gold had been given had there been any reaction.

II. Osteo-Arthritis

The group of patients with osteo-arthritis sent from the Orthopaedic Department was too small for detailed analysis. It comprised four men and two women. Unexpectedly the four male patients had nail changes. In one patient they had appeared 7 months before the arthritis, but in the remainder they were unrelated to the arthritis in its onset or course. The findings in the joints affected were typical of osteo-arthritis and bore no relation to the skin rash in time of onset or severity of symptoms.

The haemoglobin, E.S.R., and white cell counts were all normal as were the serum alkaline phosphatase levels. One patient had a serum cholesterol value of 260 mg. per 100 ml.

III. Gout and Rheumatic Fever

One patient had gout and one had a typical history of rheumatic fever. In neither were the nails affected. There were no atypical features in the arthritic or skin findings in either, and there was no obvious relation between the skin and joint manifestations.

Conclusions

The one patient with gout and the one with rheumatic fever who were examined showed no features that were not explicable on the basis of a mere coincidence of the psoriasis and the joint condition.

TABLE VI

LABORATORY INVESTIGATIONS

(Per cent. of Patients)

Serum	Cholesterol (mg./100 ml.)			Alkaline Phosphatase (K.A. Units)				Globulin (g./100 ml.)		
Amount	–180	180–215	215+	8–12	12–16	16–20	20+	2–3·6	3·6–4·0	4·0+
Psoriasis and Erosive Arthritis (32 cases)	32	65	28	26	41	22	11	57	25	17
Rheumatoid Arthritis (69 cases)	—	—	—	16	32	29	23	51	27	22

The six patients with psoriasis and osteo-arthritis were probably also examples of a chance association. The only unusual feature clinically was the nail involvement in all four male patients.

The group of patients with erosive arthritis and psoriasis show many interesting features when compared with groups having uncomplicated psoriasis and uncomplicated rheumatoid arthritis (with a positive D.A.T.).

The negative D.A.T. in 94 per cent. of these cases suggests that the combination of psoriasis and erosive arthritis is more than the coincidence of two common diseases. It suggests at least that the arthritis is modified by the presence of psoriasis, or, more probably, that it is a distinct entity. The finding of tendon sheath effusions and subcutaneous nodules (both classical manifestations of rheumatoid arthritis) in only one patient of the series—one of the two with a positive D.A.T.—lends weight to the suggestion that these two had true rheumatoid arthritis while the others formed a distinct group. There are certain distinctive features of the syndrome of psoriasis and erosive arthritis. Many of the attributes described in the literature could not be substantiated in the present series, *viz:*

(1) In the majority the psoriasis was not extensive or pustular, nor did it affect the palms and soles; when the skin eruption was extensive the arthritis was severe.

(2) Alleviation of the skin condition seemed to help the arthritis in only one case and the significance of the association was dubious since the patient was in hospital at the time.

(3) The patients did not appear unduly susceptible to toxic gold reactions.

(4) Thickening, not pitting, was the most common nail change encountered.

(5) In no case was arthritis limited to the distal interphalangeal joints.

(6) The arthritis was not unduly resistant to treatment.

(7) The serum protein levels were abnormal in several patients.

From a positive point of view the outstanding features may be summarized as follows:

(1) There was a high incidence of nail changes (87 per cent.), and these were the sites of onset in 16 per cent. Two patients had nails only affected.

(2) The nail changes bore a closer relation to the onset and course of the arthritis than the skin lesions.

(3) A small proportion (13 per cent.) appeared to show a connexion between the skin and joint manifestations as evidenced by the simultaneous onset and exacerbations.

(4) The arthritis was less often polyarticular at onset than classical rheumatoid arthritis.

(5) Distal interphalangeal joint involvement was related topographically to the nail lesions rather than to the skin lesions.

(6) Stiffness played a major part in the symptomatology.

(7) There was a high incidence of complete remissions of the arthritis.

(8) The disease was milder on the whole than rheumatoid arthritis, as shown by fewer joints involved clinically and radiographically, smaller incidence of ulnar deviation, and milder stigmata in the originally affected joints. A mutilating type does however occur rarely.

(9) The disease tends to be either very mild or crippling.

(10) A similarity to gout was noted at some time in the history in 39 per cent.

(11) When the distal interphalangeal joints and nails were involved the finger tips had a spade-like appearance.

(12) There was a marked family history of psoriasis in 35 per cent.

(13) There was a high incidence of ankylosing spondylitis.

(14) Nodules and tendon sheath effusions were absent except in one patient with a positive D.A.T.

(15) The incidence in males seemed to be slightly increased.

(16) There was apparently less anaemia, a lower E.S.R., and less tendency to leucocytosis, but this was probably due to the selection of the patients.

Summary

42 cases of psoriasis with arthritis have been studied, 34 with erosive arthritis, six with degenerative joint disease, one with gout, and one with rheumatic fever. They have been compared with 55 unselected patients with rheumatoid arthritis and a positive differential agglutination test (D.A.T.) and 310 patients with psoriasis alone. A close comparison has been made between the three groups clinically and by certain blood tests, including haemoglobin estimation, E.S.R. (Wintrobe), white cell count, serum proteins, Kunkel's zinc sulphate test, electrophoresis, serum alkaline phosphatase, serum cholesterol, C-reactive protein, and the D.A.T. It is concluded that those with osteo-arthritis, gout, and rheumatic fever were examples of a chance association, although the surprising finding of nail changes in all four male patients with osteo-arthritis is noted. On the basis of the D.A.T. it is thought that two of the group with erosive arthritis were examples of rheumatoid arthritis and coincidental psoriasis, whereas in the rest the disease probably formed a distinct entity. The significant features of the group with erosive arthritis are set out, as well as findings in the present series which are at variance with those of previous authors.

I am indebted to Dr. A. G. S. Hill, Dr. D. S. Wilkinson, Dr. M. Good, Mr. G. Platt, and other Consultants of Stoke Mandeville Hospital for allowing me to study their patients. My thanks are due especially to Dr. A. G. S. Hill and Dr. D. S. Wilkinson for their invaluable help

in the preparation and performance of this study in all its stages.

REFERENCES

Bauer, W. (1939). *New Engl. med. J.*, **221**, 524.
——, Bennett, G. A., and Zeller, J. W. (1941). *Trans. Ass. Amer. Phys.*, **56**, 349.
Bennett, G. A. (1943). *Ann. intern. Med.*, **19**, 111.
Cannon, A. B. (1934). *Arch. Derm. Syph.* (*Chicago*), **30**, 906.
Crawford, G. M. (1938). *Ibid.*, **38**, 583.
Darier, J. (1920). "A Text-book of Dermatology", ed. S. Pollitzer, p. 105. Lea and Febiger, Philadelphia.
——, Civatte, A., and Tzanck, A. (1947). "Précis de dermatologie". 5th ed., p. 147. Masson, Paris.
Dawson, M. H. (1937). *Med. clin. N. Amer.*, **21**, 1807.
——, and Tyson, T. L. (1938). *Trans. Ass. Amer. Phys.*, **53**, 303.
Empire Rheumatism Council (1950). *Brit. med. J.*, **1**, 799.
Epstein, E. (1939). *Arch. Derm. Syph.* (*Chicago*), **40**, 547.
Fawcitt, J. (1950). *Brit. J. Radiol.*, **23**, 440.
Fletcher, E., and Rose, F. C. (1955). *Lancet*, **1**, 695.
Franks, A. G., and Wallace, J. J. (1942). *Milit. Surg.*, **91**, 199.
Gribble, M. de G. (1955). *Annals of the Rheumatic Diseases*, **14**, 198.
Gross, —. (1928). *Arch. Derm. Syph.* (*Chicago*), **18**, 928.
Heller, G., Kolodny, M. H., Lepow, I. H., Jacobson, A. S., Rivera, M. E., and Marks, G. H. (1955). *J. Immunol.*, **74**, 340.
Ingram, J. T. (1954). *Brit. med. J.*, **2**, 823.
Jeghers, H., and Robinson, L. J. (1937). *J. Amer. med. Ass.*, **108**, 949.
King, E. J. (1951). "Micro-Analysis in Medical Biochemistry", 2nd ed., p. 39. Churchill, London.
Kunkel, H. G. (1947). *Proc. Soc. exp. Biol.* (*N.Y.*), **66**, 217.
Lane, C. G., and Crawford, G. M. (1937). *Arch. Derm. Syph.* (*Chicago*), **35**, 1051.
Leczinsky, C. G. (1948). *Acta derm.-venereol.* (*Stockh.*), **28**, 483.
MacKenna, R. M. B. (1950). *Brit. med. J.*, **2**, 207.
Martin, N. H., and Morris, R. (1949). *J. clin. Path.*, **2**, 64.
O'Leary, P. A. (1943). *Canad. med. Ass. J.*, **48**, 34.
Pardo-Castello, V. (1936). "Diseases of the Nails". Thomas, Springfield, Illinois.
Ragan, C., and Tyson, T. L. (1946). *Amer. J. Med.*, **1**, 252.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol.* (*N.Y.*), **68**, 1.
Sherman, M. S. (1952). *J. Bone Jt Surg.*, **34A**, 831.
Shlionsky, H., and Blake, F. G. (1936). *Ann. intern. Med.*, **10**, 537.
Sterne, E. H., and Schneider, B. (1953). *Ibid.*, **38**, 512.
Tobias, N. (1939). *New int. Clin.*, **3**, (n.s. 2), 173.
Vilanova, X., and Piñol, J. (1951). *Rheumatism*, **7**, 197.
Wassmann, K. (1949). *Annals of the Rheumatic Diseases*, **8**, 70.
White, C. J. (1938). *Urol. cutan. Rev.*, **42**, 592.

Psoriasis et arthrite

RÉSUMÉ

On étudia 42 cas de psoriasis avec arthrite, dont 34 avec arthrite érosive, 6 avec maladie articulaire dégénérative, un avec goutte et un avec rhumatisme articulaire aigu. On les compara avec 55 malades pris au hasard parmi ceux atteints d'arthrite rhumatismale confirmée par la réaction d'agglutination différentielle et avec 310 malades atteints de psoriasis seul. On fit une comparaison étroite entre les trois groupes du point de vue clinique et de laboratoire, y compris: taux d'hémoglobine, vitesse de la sédimentation globulaire (Wintrobe), numération leucocytaire, taux des protéines sériques, test de Kunkel au sulfate de zinc, électrophorèse, phosphatase alcaline sérique, cholestérol sérique, protéine C-réactive et réaction d'agglutination différentielle. On conclue que les cas d'ostéo-arthrite, de goutte et de rhumatisme articulaire aigu étaient des exemples d'association fortuite, bien qu'on note la découverte surprenante des altérations unguéales chez tous les quatre ostéo-arthritiques mâles. Sur la base de la réaction d'agglutination différentielle on pense que dans deux cas d'arthrite érosive le rhumatisme et le psoriasis coëxistaient par hasard, alors que dans les autres la maladie formait probablement une entité distincte. On souligne les caractères significatifs du groupe atteint d'arthrite érosive ainsi que les résultats dans la série présente qui ne s'accordent pas avec ceux obtenus par des auteurs antérieurs.

Psoriasis y artritis

SUMARIO

Se estudiaron 42 casos de psoriasis con artritis, entre ellos 34 con artritis erosiva, 6 con enfermedad articular degenerativa, uno con gota y uno con reumatismo articular agudo. Se compararon estos casos con otros 55 de artritis reumatoide tomados al azar y confirmados por la reacción de aglutinación diferencial y con 310 casos de psoriasis sola. Estos tres grupos fueron comparados estrechamente desde el punto de vista clínico y de laboratorio, con determinación de hemoglobina, velocidad de la sedimentación eritrocitaria (Wintrobe), recuento leucocitario, proteinas séricas, test de Kunkel con sulfato de cinc, electroforesis, fosfatase alcalina sérica, colesterol sérico, proteina C-reactiva y reacción de aglutinación diferencial. Se concluye que los casos de osteo-artritis, de gota y de reumatismo articular agudo fueron ejemplos de asociación fortuita, aunque se nota el hallazgo sorprendiente de alteraciones de las uñas en los cuatro hombres con osteo-artritis. Los resultados de la reacción de aglutinación diferencial hacen presumir una asociación fortuita entre la psoriasis y el reumatismo en dos casos de artritis erosiva, mientras que en los demás casos se trataría de una entidad distinta. Se subrayan los rasgos significativos del grupo con artritis erosiva así como los resultados en la serie presente que no se acuerdan con los obtenidos por otros autores.

Ann. rheum. Dis. (1956), **15**, 357.

STUDIES OF HYALURONIC ACID IN RHEUMATOID ARTHRITIS

BY

N. EGELIUS, E. JONSSON, AND L. SUNDBLAD

From the Medical Department III and the Central Laboratory, Södersjukhuset, Stockholm, Sweden

(RECEIVED FOR PUBLICATION JULY 4, 1956)

It has previously been shown that in most joint diseases changes occur in the hyaluronic acid in the joint fluid. In diseased fluids the hyaluronic acid has a considerably lower degree of polymerization than in normal fluids or in uncomplicated traumatic effusions (Sundblad, 1953).

The hyaluronic acid changes are especially marked in rheumatoid arthritis. We recently demonstrated (Sundblad, Egelius, and Jonsson, 1954) that the clinical response to the intra-articular injection of hydrocortisone is regularly accompanied by an often complete restoration to normal of the hyaluronic acid changes.

It appeared to us that determination of the degree of polymerization of the hyaluronic acid might provide a convenient objective record of the effects of therapy in joint diseases. The present study includes comparative tests with hydrocortisone acetate, hydrocortisone *tertiary*-butylacetate and other forms of local or systemic therapy. A brief discussion of the nature of the hyaluronic acid changes and their relation to certain clinical and laboratory data is also given.

Methods

Synovial Fluid.—Sterile samples were stored at −20° C. if not analysed immediately. After centrifugation the fluids were diluted with phosphate-NaCl buffer (*p*H 7, ionic strength 0·20) before determination of viscosity.

Degree of Polymerization of Hyaluronic Acid.—Hyaluronic acid is composed of units of N-acetyl-glucosamine and glucuronic acid linked together to form highly polymerized molecules. Because of their molecular complexity, the solutions show a high viscosity even at small concentrations. Thus almost all of the viscosity of the synovial fluid is due to the hyaluronic acid. A further characteristic is the marked flow anomalies, in that pronounced alterations in the viscosity occur with changes of pressure. The so-called intrinsic viscosity (the ratio of viscosity to concentration in dilute solutions extrapolated to zero concentration) and the degree of anomalous viscosity are related to the average molecular size. They may be used as an index of the polymerization degree.

The anomalous viscosity test has been employed in the present investigation. This is more sensitive than the determination of the intrinsic viscosity and has the further advantage that no estimation of hyaluronic acid concentration is required. The method used has been previously described by Sundblad (1954). The anomalous viscosity (A) is directly calculated from two determinations of viscosity N_{sp} in the same capillary micro-viscometer, using two different pressures (maximum stresses of 7 and 17 dynes per cm.^{2}) as:

$$A = \log \frac{(N_{sp})_7 \cdot [1 + 0{\cdot}16\ (N_{sp})_{17}]}{(N_{sp})_{17} \cdot [1 + 0{\cdot}16\ (N_{sp})_7\ ]}$$

The values of $\frac{N_{sp}}{1 + 0{\cdot}16\ N_{sp}}$ corresponding to the values of N_{sp} are conveniently taken from graphs. N_{sp} is the specific viscosity of the hyaluronic acid. Corrections were thus made for protein viscosity, determined after complete degradation of the hyaluronic acid by incubating the samples with hyaluronidase. To avoid decimals the values of A are given as $A \times 10^3$. In normal joint fluids the values for $A \times 10^3$ exceed 80 (Sundblad, 1953, 1954).

Material

Altogether about 500 samples of joint fluid were analysed by the method described. The majority of the patients from which the fluid samples were taken suffered from rheumatoid arthritis, the rest of them from various forms of other joint diseases. The present paper deals with the cases of rheumatoid arthritis and osteo-arthritis (about 400 samples of fluid from 134 cases). A few *post-mortem* fluids were also analysed. Most of the samples were obtained by knee puncture. In some cases several joints were examined in the same patient.

TABLE I

RESPONSE TO DIFFERENT INTRA-ARTICULAR AGENTS OF THE ANOMALOUS VISCOSITY INDEX (A × 10^3), 2 TO 3 DAYS AFTER INJECTION

Treatment	Dosage (mg.)	Number of Cases	Average Initial Value of A × 10^3	Response: Average Change in A × 10^3 2 to 3 days after Injection	Significance *P*
Hydrocortisone acetate	25–50	30	50·1	+24·3	<0·001
Hydrocortisone *tertiary*-butylacetate	25–50	11	55·1	+20·2	<0·001
Cortisone	50	5	55·2	+ 7·4	<0·05
Phenylbutazone	600	10	49·1	− 3·1	

Results

(1) Intra-Articular Injections of Corticosteroids and Other Agents in Cases of Rheumatoid Arthritis.—We previously showed (Sundblad and others, 1954) that the effect on the hyaluronic acid of intra-articular hydrocortisone is at its peak 2 to 3 days after injection. In Table I we have compared different agents with respect to the initial effect.

Table I shows that only agents with clinically proved local effect influence the hyaluronic acid. Treatment with hydrocortisone preparations was followed by increased values of anomalous viscosity in all cases, although the variation was comparatively great. In half the cases the values had returned to roughly normal after 2 to 3 days. Further analysis of the cases treated with hydrocortisone did not indicate any difference in biochemical response to injections of 25 or 50 mg. The average increase in fourteen cases given 25 mg. was 26·2 as compared with 22·5 in 27 cases given 50 mg.

Duration of Effect.—In Fig. 1 the effect of hydrocortisone acetate is compared with that of hydrocortisone *tertiary*-butylacetate. In a preliminary publication (Egelius, Jonsson, and Sundblad, 1955) we stated that the average duration with hydrocortisone *tertiary*-butylacetate appeared to be longer than with hydrocortisone acetate. These results

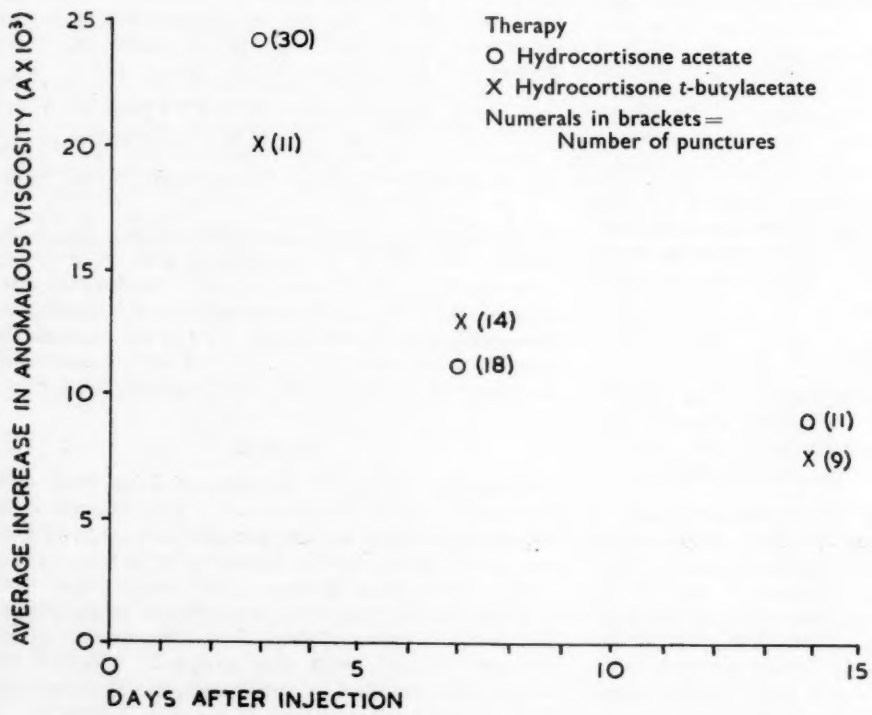


Fig. 1.—Average increase in anomalous viscosity of the synovial fluid in two series of patients with rheumatoid arthritis. Thirty were given hydrocortisone acetate and fourteen were given hydrocortisone *tertiary*-butylacetate. The number of fluids tested after 3, 7, and 14 days are shown in brackets.

agreed with the clinical observations made by Hollander, Brown, Jessar, and Brown (1954). However, no significant difference was found between the two preparations.

In certain cases efforts were made to increase the initial effect and the duration by the repeated administration of hydrocortisone acetate at intervals of from 1 to 2 days, but nothing appeared to be gained by this procedure. In three cases 600 mg. phenylbutazone was given every second day four to six times without any clinical or biochemical effect. On the contrary, in some cases we noted a significant drop in the anomalous viscosity values after intra-articular phenylbutazone injections. Probably this is due to a chemical synovitis, clinically demonstrated in these cases by increase in pain and exudation.

Action of Hydrocortisone on Hyaluronidase.—It has been shown by Ekman, Thune, and Truedsson (1953) that, after repeated intra-articular injections of cortisone, there is an increase in the hyaluronidase inhibitor level in the joint fluid. Furthermore, Hahn, Thune, and Truedsson (1952) claimed to have shown a therapeutic effect of hyaluronidase inhibitor therapy in rheumatoid arthritis. On the other hand, the serum inhibitor level is known to decrease after ACTH therapy.

We have made a series of experiments to study the possible relationship between the local action of hydrocortisone and hyaluronidase or anti-hyaluronidase factors. As previously reported, we demonstrated a *decrease* in hyaluronidase inhibitor activity in the joint fluids 2 days after hydrocortisone administration. Intra-articular injections of high doses of a potent hyaluronidase inhibitor (polyphloretin phosphate*) did further not influence the hyaluronic acid conditions (Sundblad and others, 1954).

In two patients, the administration of hyaluronidase or hyaluronidase inhibitor together with hydrocortisone did not appear to influence the response to the hormone (Fig. 2), and it seemed unlikely that the action of hydrocortisone on the hyaluronic acid was mediated by any influence on the hyaluronidase factors.

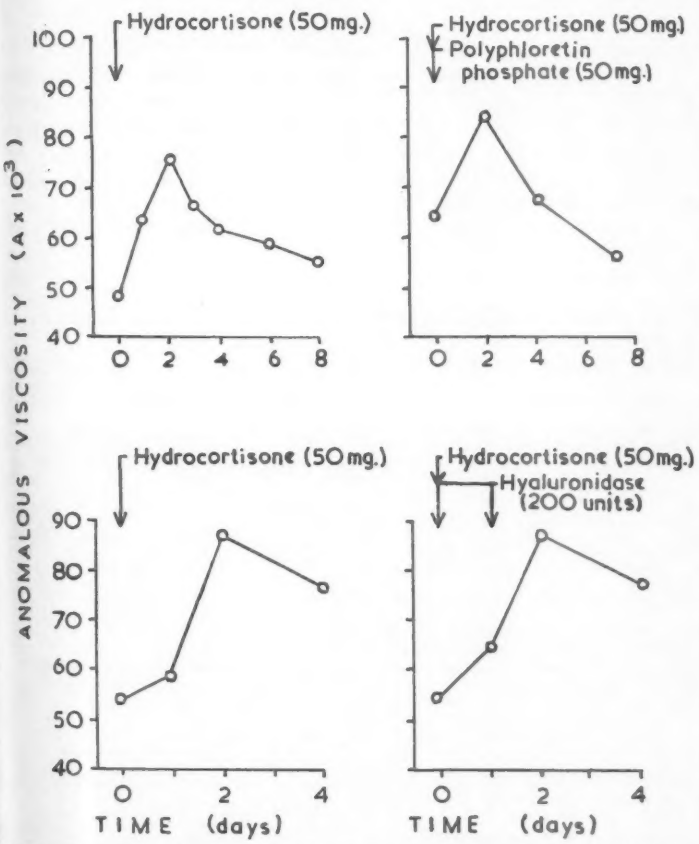


Fig. 2.—Anomalous viscosity levels in two female patients (A and B) after the injection of hydrocortisone, hyaluronidase, and hyaluronidase inhibitor. In each experiment the initial increase was followed by a steady fall.

A few experiments of theoretical interest in this connexion may be briefly mentioned. An antagonism between vitamin B_{12} and hydrocortisone upon carbohydrate metabolism has been supposed by Lövgren, Norman, and Winqvist (1955). In a case of rheumatoid arthritis with bilateral knee-joint effusions, we injected into one knee 25 mg. hydrocortisone and 25 μg. vitamin B_{12} and into the other knee hydrocortisone only. The change in anomalous viscosity obtained after 2 days was the same in both knees.

Boström, Rodén, and Vestermark (1955) have shown that glutamine may play an important role in the biosynthesis of the mucopolysaccharides. In view of this we recently started some experiments with the intra-articular administration of glutamine. So far no significant effect upon the hyaluronic acid has been noted.

(2) Systemic Therapy.—The hyaluronic acid changes were observed in three cases of rheumatoid arthritis treated with oral hydrocortisone (maximum dosage 80 mg. daily). All three patients showed a comparatively slight clinical response

* Leo Ltd.

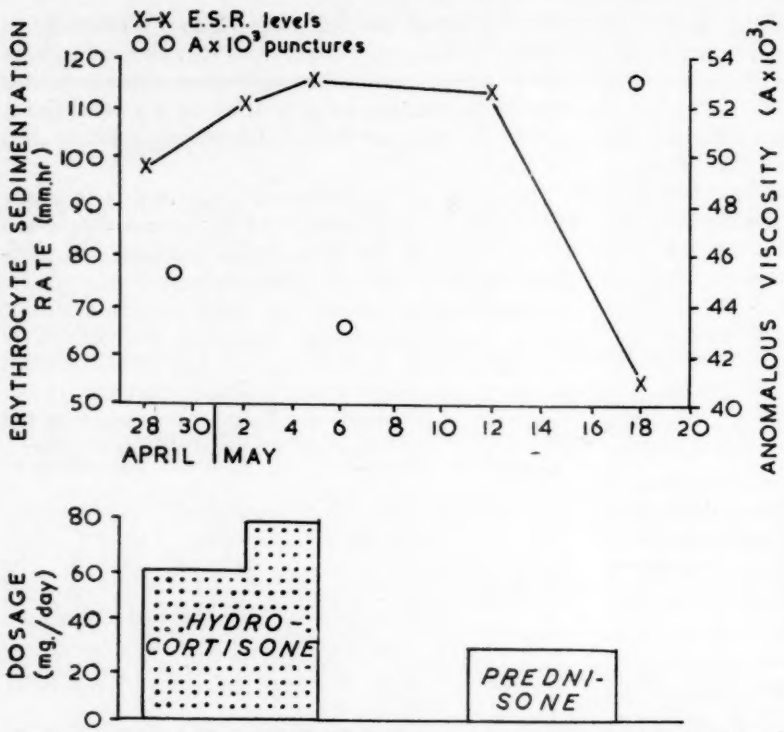


Fig. 3.—Anomalous viscosity level and erythrocyte sedimentation rate in a female aged 59 with rheumatoid arthritis treated with hydrocortisone and prednisone.

with only moderate changes in the erythrocyte sedimentation rate. The change in anomalous viscosity was slight (average initial value $A \times 10^3 = 50{\cdot}5$; average change $+ 4{\cdot}5$). In one of these cases we exchanged the hydrocortisone for prednisone 30 mg. daily, and the anomalous viscosity values increased by 23 per cent. (Fig. 3), and the clinical effects were also satisfactory. Good effects with 20 mg. prednisone daily were also obtained in another case which showed a maximum increase of 43 per cent. (Fig. 4).

In three cases treated with 5-6 g. salicylic acid daily, only very slight changes in anomalous viscosity were noted (average initial value $A \times 10^3 = 48{\cdot}2$; average change $-1{\cdot}2$).

(3) Miscellaneous.—In eight cases the effect of various forms of physiotherapy (short wave diathermy four cases, radar two cases, and hot mud two cases) was tested by repeated joint

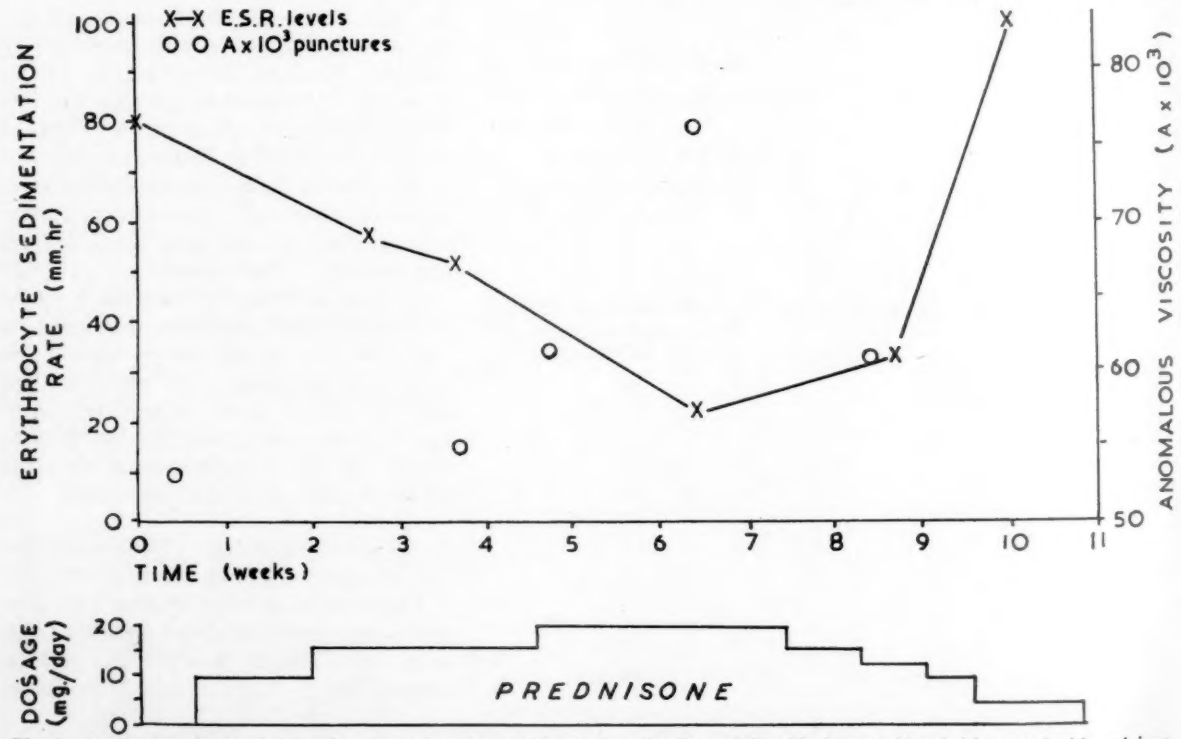


Fig. 4.—Anomalous viscosity level and erythrocyte sedimentation rate in a female aged 53 with rheumatoid arthritis treated with prednisone.

punctures. In no case was any significant change in the anomalous viscosity noted (average initial value 45·9; average change + 1·7).

Finally we examined three cases treated with *x*-ray therapy. In one we noted a significant and lasting increase in anomalous viscosity, but this should probably be ascribed to a spontaneous remission of the disease.

(4) Nature of Hyaluronic Acid Changes.—The clinical and laboratory data of 119 cases of rheumatoid arthritis were analysed by the following criteria:

(*a*) Sex and age,
(*b*) Type of onset according to the classification of Egelius, Hävermark, and Jonsson (1949),
(*c*) Stage of disease according to the classification of Steinbrocker, Traeger, and Batterman (1949),
(*d*) Evidence of bone destruction,
(*e*) Erythrocyte sedimentation rate,
(*f*) Haemoglobin value,
(*g*) C-reactive protein in blood and joint fluid,
(*h*) Sensitized sheep-cell agglutination test,
(*i*) Streptococcal agglutination and antistreptolysin titres.

There were no significant correlations between these data and the hyaluronic acid changes, but the viscosity values tended to be lower in early cases, in cases without bone destruction, and in younger patients.

Since the presence of osteo-arthritis in older patients might have influenced the results, we analysed fifteen fluids from cases of osteo-arthritis. The average of $A \times 10^3$ was 53·5 as compared with 51·4 in the 119 cases of rheumatoid arthritis. Thus there was no essential difference between these two conditions ($d = 2{\cdot}1$; $t = 0{\cdot}58$; $P > 0{\cdot}1$). Similar results have been reported by Sundblad (1953) in determinations of intrinsic viscosity, and more recently by Fletcher, Jacobs, and Markham (1955) in the anomalous viscosity test.

No correlation was found between the hyaluronic acid changes and the activity of the disease as judged by conventional criteria. This did not support the idea of a general type of hyaluronic acid disturbance. On the other hand fluids obtained from both knees in cases with bilateral knee joint effusions were often remarkably similar with respect to hyaluronic acid changes.

To examine the problem further we compared the anomalous viscosity indices of affected and unaffected joints in four patients with rheumatoid arthritis (*post-mortem* puncture in one case; amounts of fluid in the affected joints not measurable in another). The results are shown in Table II, and are also compared with the indices of fluids taken from normal persons (not affected by joint disease) obtained by punctures performed as soon as possible *post-mortem*. We were not inclined to perform *in vivo* punctures on healthy persons.

The results given in Table II show that in the cases of rheumatoid arthritis the degree of hyaluronic acid changes differed widely between the affected and unaffected joints, but that in different joints in the control cases it was essentially the same. From the data of intrinsic viscosity in normal joint fluids given by Sundblad (1953) and the correlation between anomalous viscosity and intrinsic viscosity (Sundblad, 1954), a probable range of values of $A \times 10^3$ in normal human fluid would be 80 to 100. This agrees with the findings in the *post-mortem* fluids in Table II. In spite of the small number of cases it seems justified to conclude that in clinically normal joints in rheumatoid arthritis the hyaluronic acid has a normal degree of polymerization. Accordingly the hyaluronic acid changes in affected joints must be due to local connective tissue disturbance.

TABLE II

COMPARISON OF THE ANOMALOUS VISCOSITY INDICES ($A \times 10^3$) IN THE AFFECTED AND CLINICALLY NORMAL JOINTS OF FOUR PATIENTS WITH RHEUMATOID ARTHRITIS AND IN SELECTED JOINTS OF FOUR CONTROLS

Case No.		Sex	Age (yrs)	Clinical Findings	Typical *x* ray	Stage of Disease	E.S.R. (mm./hr)	Unaffected Joints	$A \times 10^3$	Affected Joints	$A \times 10^3$
Rheumatoid Arthritis	1*	M	39	Iritis. Death in uraemia due to amyloidosis	Yes	II	123	R. knee R. hip	85·1 73·6	L. knee	10·6
	2	M	61	Waaler-Rose 1/160	Yes	III	56	L. knee	83·9	L. wrist L. ankle	too low to measure
	3	F	45	—	Yes	III	19	R. knee	93·6	L. 2mcp	51
	4	F	48	Waaler-Rose 1/40	No	II	30	L. knee	82·6	R. knee	48·7
Controls (No Joint Disease)	5*	F	15	Acute tracheo-bronchitis and pneumonia				R. hip	85		
	6*	M	35	Myocardial infarction				R. hip R. knee	84·6 88·9		
	7*	M	74	Bronchopneumonia and cardiosclerosis				R. hip	85·2		
	8*	M	50	Congenital heart disease. Death in heart failure				L. hip R. knee	91·7 85·9		

* *Post-mortem* punctures.

Summary

Determination of the degree of polymerization of the synovial hyaluronic acid provides a convenient method of recording objectively the effects of treatment of rheumatoid arthritis. Hyaluronic acid changes can easily be estimated by determining the changes in viscosity of the synovial fluid. No determination of hyaluronic acid concentration is required.

Intra-articular administration of both hydrocortisone acetate and hydrocortisone *tertiary*-butylacetate restored the hyaluronic acid changes almost to normal within 2 to 4 days. After a single injection the average duration of effect was 2 to 3 weeks. In this respect no definite difference could be established between the two preparations. There was no obvious difference between the response to doses of 25 mg. and that to doses of 50 mg.

Intra-articular cortisone caused only a slight effect and phenylbutazone none at all.

No effect was obtained with physical therapy, *x*-ray therapy, or salicylates.

The systemic administration of hydrocortisone or prednisone produced variable effects which roughly paralleled the clinical response. Only a few cases were tested.

A series of experiments demonstrated that hydrocortisone does not appear to influence the hyaluronidase or anti-hyaluronidase factors. The effect of the hormone on the hyaluronic acid is probably due to anti-inflammatory action on the perisynovial connective tissue.

In a series of 119 cases of rheumatoid arthritis there was no significant correlation between the activity of disease and the degree of hyaluronic acid changes in the synovial fluid. In clinically normal joints the degree of polymerization of the hyaluronic acid was normal. These findings suggest that the hyaluronic acid changes in affected joints are unlikely to be due to a general disturbance of hyaluronic acid metabolism.

REFERENCES

Boström, H., Rodén, L., and Vestermark, A. (1955). *Nature (Lond.)*, **176**, 601.

Egelius, N., Hävermark, N. G., and Jonsson, E. (1949). *Annals of the Rheumatic Diseases*, **8**, 217.

——, Jonsson, E., and Sundblad, L. (1955). "Proc. III European Rheumatology Congress." In the press.

Ekman, B., Thune, S., and Truedsson, E. (1953). *Scand. J. clin. Lab. Invest.*, **5**, 175.

Fletcher, E., Jacobs, J. H., and Markham, R. L. (1955). *Clin. Sci.*, **14**, 653.

Hahn, L., Thune, S., and Truedsson, E. (1952). *Annals of the Rheumatic Diseases*, **11**, 272.

Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., and Brown, C. Y. (1951). *J. Amer. med. Ass.*, **147**, 1629.

Lövgren, O., Norman, A., and Winqvist, G. (1955). *Acta rheum. scand.*, **1**, 106.

Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

Sundblad, L. (1953). *Acta Soc. Med. upsalien.*, **58**, 113.

—— (1954). *Scand. J. clin. Lab. Invest.*, **6**, 288.

——, Egelius, N., and Jonsson, E. (1954). *Ibid.*, **6**, 295.

Etudes de l'acide hyaluronique dans l'arthrite rhumatismale

RÉSUMÉ

La détermination du degré de polymérisation de l'acide hyaluronique synovial fournit une méthode pratique pour enrégistrer objectivement les effets du traitement de l'arthrite rhumatismale. Les altérations de l'acide hyaluronique peuvent être aisément estimées par la détermination des modifications de la viscosité du liquide synovial. La détermination du taux d'acide hyaluronique n'est pas nécessaire.

L'injection intra-articulaire aussi bien d'acétate de hydrocortisone que de butylacétate tertiaire d'hydrocortisone ramenait l'état de l'acide hyaluronique presqu'à la normale en l'espace de 2 à 4 jours. Après une seule injection, la durée moyenne de l'effet produit était de 2 à 3 semaines. De ce côté-ci on ne pouvait mettre en évidence aucune différence entre les deux préparations. Il n'y avait pas de différence marquée entre la réponse à des doses de 25 mg. et celle à des doses de 50 mg.

La cortisone intra-articulaire ne produisait qu'un effet léger et la phényl-butazone n'en produisait aucun.

Le traitement physique, aux rayons *X* et salicylé, fut sans effet.

L'administration générale d'hydrocortisone ou de prednisone produisait des effets variables, plus ou moins parallèles à la réponse clinique. Seuls quelques cas furent étudiés.

Une série d'expériences montra que l'hydrocortisone ne semble pas influencer les facteurs hyaluronidase et antihyaluronidase. L'effet de l'hormone sur l'acide hyaluronique est probablement dû à une action anti-inflammatoire du tissu conjonctif périsynovial.

Dans une série de 119 cas d'arthrite rhumatismale, il n'y eut pas de corrélation significative entre l'activité de la maladie et l'importance des altérations de l'acide hyaluronique dans le liquide synovial. Dans les articulations cliniquement normales, le degré de polymérisation de l'acide hyaluronique était normal. Ces résultats suggèrent que les altérations de l'acide hyaluronique dans les articulations malades ne seraient pas dues à un dérangement général du métabolisme de l'acide hyaluronique.

Estudios del ácido hialurónico en la artritis reumatoide

SUMARIO

La determinación del grado de polimerización del ácido hialurónico sinovial provee un método práctico para registrar objetivamente los efectos del tratamiento de la artritis reumatoide. Las alteraciones del ácido hialurónico se pueden seguir fácilmente al determinar los cambios en la viscosidad del líquido sinovial. La determinación de las cifras del ácido hialurónico no es necesaria.

Inyecciones intra-articulares tanto de acetato de hidrocortisona como de butilacetato terciario de hidrocortisona restablecían el ácido hialurónico a su estado casi normal dentro de 2 a 4 días. Después de una sola inyección el efecto duraba por término medio de 2 a 3 semanas. En este respecto no se pudo evidenciar diferencia alguna entre las dos preparaciones. Tampoco

hubo diferencia obvia entre el efecto de una dosis de 25 mg. y él de una dosis de 50 mg.

La cortisona intra-articular no produjo más que un efecto ligero; la fenilbutazona fué sin efecto.

Fisioterapia, radioterapia y salicilatos no tuvieron efecto alguno.

La administración general de hidrocortisona o de prednisona produjo efectos variables, más o menos paralelos a la respuesta clínica. Pocos casos fueron investogados.

Una serie de experimentos muestra que la hidrocortisona no parece influir en los factores hialuronidase y antihialuronidase. El efecto de la hormona sobre el ácido hialurónico se debe probablemente a una acción anti-inflamatoria del tejido conjuntivo perisinovial.

En una serie de 119 casos de artritis reumatoide, no hubo correlación significativa entre la actividad de la enfermedad y la importancia de las alteraciones del ácido hialurónico en el líquido sinovial. En articulaciones clínicamente normales, el grado de polimerización del ácido hialurónico fué normal. Estos resultados sugieren que las alteraciones del ácido hialurónico en las articulaciones enfermas no se deben a un desarreglo general del metabolismo del ácido hialurónico.

Ann. rheum. Dis. (1956), **15**, 364.

RESPONSE BY ANTIBODIES TO TISSUE ANTIGENS IN THE COURSE OF RHEUMATIC FEVER

BY

V. WAGNER AND V. REJHOLEC

STATISTICAL EVALUATION BY V. MALY

TECHNICAL ASSISTANCE BY A. SOVAKOVA, M. MOTLIKOVA, E. HALLEROVA

From the Institute of Medical Microbiology, Charles University, Plzen, the Research Institute of Rheumatic Diseases, Prague, and the Institute of Public Health Organization, Charles University, Prague

(RECEIVED FOR PUBLICATION AUGUST 13, 1956)

Weintraud (1913) was the first to envisage the possibility that tissue alterations in rheumatic patients may be due to a pathogenic anaphylactic reaction, but at that time it was not possible to verify his hypothesis by laboratory tests. The toxic properties of sera from rheumatic fever patients were first experimentally demonstrated by Ramsdell and Davidsohn (1930), and Klujeva and Bobritzkaja (1934). Brokman, Brill, and Frendzel (1937) found in the sera of rheumatic patients antibodies which gave a complement-fixation reaction with organs from children who had died with rheumatism. Coburn and Pauli (1939) found in the sera of patients in the acute stage of rheumatic fever a precipitin which reacted to an antigen which had been present in the blood before the onset of the attack. Their findings were partially corroborated by Wedum and Wedum (1946), but were questioned by Fischel and Pauli (1949).

Auto-antibodies to an aqueous extract of myocardium were demonstrated by Cavelti (1945) by means of collodion particle agglutination in a high proportion of rheumatic fever cases. Lippman, Cameron, and Campbell (1950) detected them in the sera of nephritic patients and proved their cytotic effects on myocardial tissue cultures. Lansbury, Crosby, and Bello (1950) found in the sera of patients with rheumatoid arthritis antibodies which would bind with extracts from pathological and normal tissues. Rejholec, Vančura, Wagner, and Mandlikova (1952) demonstrated antibody to myocardium in the blood of nephritic patients by means of collodion particle agglutination; Rejholec, Wagner, and Mandlikova (1952) and Rejholec and Wagner (1955) also showed them by the same method in patients with rheumatic fever. Osler, Hardy, and Sharp (1954), using alcoholic extract of human heart for antigen, observed complement-fixation reactions in 50 per cent. of rheumatic patients, but also in 20 per cent. of controls. Vorlaender (1952), and Vorlaender, Fitting, and Blankenheim (1954) demonstrated auto-antibodies in several patients with rheumatic fever by the technique of absorption and haemagglutination of erythrocytes sensitized with artery-wall antigen. They observed a certain parallelism with the course of the disease, although the number of their cases was small. Their findings were positive in the subchronic stage of the disease and negative in the acute phase. Steffen (1954a, b), Steffen and Rosak (1955), and Steffen and Schindler (1955) developed an indirect serological method of demonstrating auto-antibodies to connective tissue in rheumatism by absorbing the antiglobulin serum.

On the other hand, Fischel and Pauli (1949) failed to find antibody in rheumatism by the technique of collodion particle agglutination. It should be noted that Cavelti himself and subsequent investigators (McKee and Swineford, 1951; Peck and Thomas, 1948; Humphrey, 1948) were unable to repeat his work.

The present investigation was undertaken to verify the finding of auto-antibodies in the course of rheumatic fever, and to establish whether there is an interdependence between the clinically demonstrable involvement of different organs and tissues and the occurrence of antibody, and whether the presence and the level of auto-antibodies may serve as an index of disease activity. Blood samples were tested at short intervals during periods of hospitalization for the presence of antibodies to five types of tissue. The results were then compared with parallel clinical observations.

Material and Methods

Preparation of Antigens.—Tissues for antigen extraction were taken from dead bodies, preferably those killed by accident; those dying from infection were excluded. The time expired since the death is of importance; it must not exceed 18 hours, and the body must be kept at 4° C. Like Lange, Gold, and Weiner (1949) we obtained the best results with tissues from children and juveniles. We selected those types of tissue which most frequently suffer in the course of the rheumatic process: myocardium ("M"), valves with connective tissue of the heart ("V"), subcutaneous tissue ("ST"), skin ("S"), and joint capsule ("JC").

The tissues were minced and each small portion was stored in a separate container at −18° C. Only one container at a time was taken from the refrigerator for processing, and it was never used for longer than one day. Thus we avoided the repeated freezing and unfreezing of tissues which in our experience influences the stability of tissue antigen very unfavourably. At −18° C. the tissues could be kept unspoiled for weeks and even months.

After unfreezing, the tissues were ground aseptically. The homogenate was suspended in a 1 : 40 solution (Wagner, 1954), always freshly prepared and composed of 9·6 g. NaCl, 0·4 g. $CaCl_2$, and 0·1 g. $NaHCO_3$,* with the addition of redistilled water up to 1,000 ml. After vigorous shaking, the suspension was incubated for 15 minutes at room temperature and then centrifuged. The supernatant fluid, slightly opalescent, was mixed in equal parts with a collodion suspension prepared by the method of Cavelti (1947), and diluted by addition of a saline solution as above; the final density of the collodion suspension was equal to Degree 2 of the scale described by McFarland (1907). The nitrocellulose for the preparation of collodion particles had to be of Grade 22 viscosity, measured by the Wassag method (other grades proved unsuitable).† The mixture of collodion suspension and antigen was incubated at room temperature for 1 hour.

Before being used in experiments, each tissue extract was tested with several sera of normal humans (blood donors), as well as with a diagnostic Group O serum possessing a titre of at least 1 : 256. Only those tissues which had proved stable in these preliminary tests were used in the experiments proper. Sometimes only one out of many cadavers gave antigens suitable for collodion agglutination. The least stable antigens were those from the cardiac valves with connective tissue of the heart.

Agglutination Tests.—Serum dilutions in serial two-fold steps, from 1 : 2 to 1 : 256, were made with the same saline solution in tubes of an inner diameter of about 8 mm. To every serum dilution of volume 0·25 ml. was added an equal volume of collodion particles coated with antigen. After vigorous shaking, incubation lasting 90 min. at room temperature, and centrifugation at 1,500 r.p.m. for 3 min., the reactions were read while the upper part of the tube was lightly held and the base gently tapped to stir up the sediment. The dilution which showed an agglutination visible to the naked eye, even if only slightly granular, was recorded as the final titre.

Control Tests.—The following tests were always carried out in the same conditions:

(1) With bare collodion particles mixed with isotonic saline instead of serum;

(2) With collodion particles coated with antigen and mixed with saline;

(3) With collodion particles coated with antigen and mixed with a negative serum—the last-named tests were done in each series of examinations with several sera from different blood donors and healthy members of the sanitary staff—diluted as in the test proper;

(4) With collodion particles without antigen, mixed with the serum from a rheumatic patient, similarly diluted.

The results of the tests proper were recorded and used for the final evaluation, provided no agglutination could be detected in any of the control tests.

All the serological tests were carried out by one of us (W.V.) in ignorance of the diagnosis and the clinical state of the patient.

Blood Samples for Processing.—These were drawn from the cubital vein. The serum was separated from the clot aseptically as soon as possible upon coagulation. The patients' sera were stored at −25° C. and dispatched by train once a week to the laboratory; the temperature at which they were kept on the journey, which lasted for about 24 hrs, was outside our control. The control sera were stored directly in the laboratory.

Selection and Examination of Patients.—38 patients (20 male and 18 female) were hospitalized in the wards of the Research Institute of Rheumatic Diseases, Prague, between February, 1954, and June, 1955, with the diagnosis of rheumatic fever. Four of them were hospitalized twice in this period and have been listed in some of our Tables as two independent cases, making a total of 42. The average age of the women was 18 years (range 10 to 39) and of the men 17 (range 6 to 43).

The diagnosis had been made by accepted criteria on the basis of past history, objective clinical examination, and several laboratory tests, and was constantly checked during the course of the disease.

The patients were first examined on the day of admission, before the institution of therapy. On this day, blood samples for the serological tests and for the erythrocyte sedimentation rate and Weltman reaction were taken, an electrocardiograph was made, the temperature was recorded, and a nasopharyngeal swab was taken for bacteriological tests. In taking the medical history, special stress was put on the chronological sequence of the preceding infectious phase, the first signs of rheumatic fever, and the treatment before admission.

* These chemicals were of the Lachema, Brno, make, and of the pro analysi grade.

† We employed nitrocellulose E 620 produced by Explosia, Semtin, Czechoslovakia. The collodion described in the Pharmacopoeia gave markedly inconsistent results.

Thirty patients were undergoing a first attack; the rest the second or a late acute episode.

Twenty patients had not been treated at all before admission, not even by rest in bed. In this group, the average interval between the first signs of rheumatic fever and hospitalization was 10·4 days (three cases 2 days, two cases 3 days, seven cases 4 to 7 days, five cases 8 to 14 days, three cases longer than 14 days).

Eight patients had been treated before hospitalization by rest in bed and anti-rheumatic medicaments in insufficient doses (less than 5 g. sodium salicylate or less than 1 g. amidopyrin daily). In this group, the mean interval between the first signs of disease and hospitalization was 14 days and the average duration of medication 11·5 days.

Seven patients had been treated by full doses of salicylate or amidopyrin and by absolute rest in bed. The average interval between the onset of disease and hospitalization was 16 days, including an average of 14 days' adequate therapy.

Seven patients who had been transferred from other hospitals were all in a late stage of the disease.

Treatment

Strictly controlled rest in bed was maintained till the signs of disease activity subsided.

Salicylate.—26 patients received appropriate doses, which in the acute phase were never less than 10 g. in 24 hrs.

Amidopyrin.—Seven patients received daily doses of at least 2 g.

For nine patients these two drugs were combined or alternated, owing especially to the intolerance of salicylate.

Hormone Therapy.—This was instituted in five patients in whom the salicylate or amidopyrin therapy seemed contra-indicated or proved inefficient or was not supported. In three cases ACTH was administered and in two oral cortisone. No patient was treated exclusively with hormones.

Antibiotics.—Penicillin or other antibiotics were given sixteen times, solely to suppress the symptoms of the infection of upper respiratory tracts or upon detection of beta-haemolytic streptococcus in the nasopharyngeal mucus.

In all cases the treatment given to the patients during hospitalization may thus be regarded as adequate, in spite of certain individual differences in dosage and type of medicament. None of the patients was given digitalin at any stage.

Results

In the course of the present investigation, 307 blood samples from rheumatic patients in different stages of disease and several hundred blood samples from normal persons were examined. The last-mentioned showed no positive reaction whatever.

Fig. 1 shows percentages of patients with positive findings of auto-antibodies to individual antigens, irrespective of their level. The findings are charted in periods of 4 days, beginning with the day when therapy was started in the ward. The results obtained with skin antigen are omitted, as they resemble very closely those obtained with subcutaneous tissue. The average erythrocyte sedi-

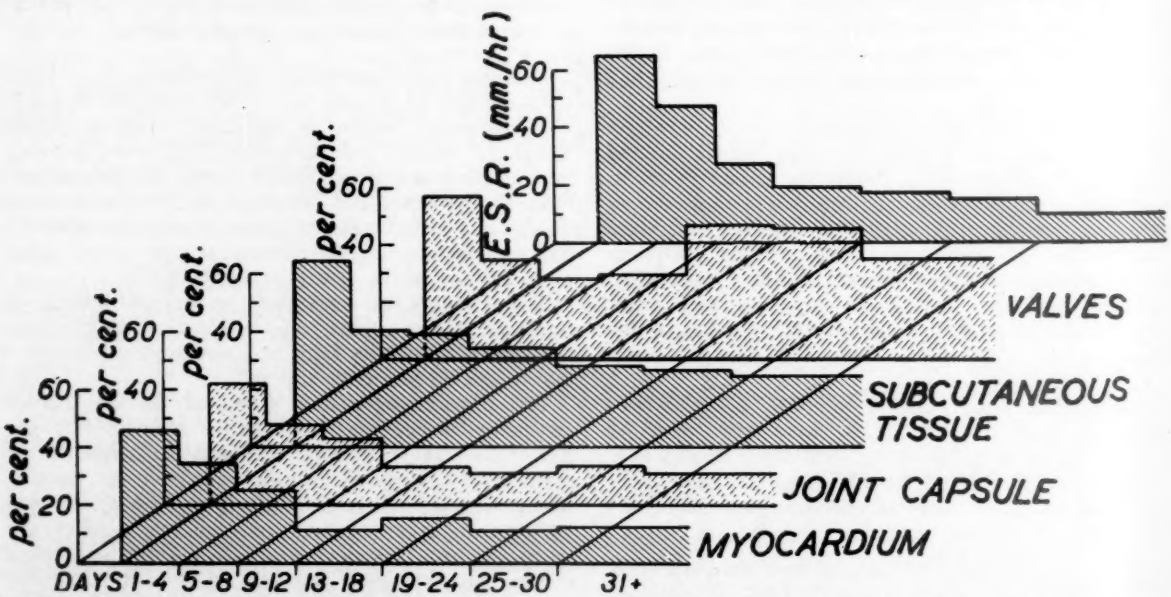


Fig. 1.—Percentages of patients showing auto-antibodies (at whatever level) to different antigens in periods of 4 days, and, for comparison, mean erythrocyte sedimentation rates from the same blood samples.

mentation rate in the first hour is also given for comparison.

The total from which the percentages were computed was not a constant, but decreased steadily especially after the 19th day, owing to the gradual discharge of healed patients. Thereafter, the total consisted of patients who had suffered a re-infection or in whom the results of medication were not satisfactory.

The rate of positive reactions to individual antigens in the first few days after admission was between 40 and 60 per cent. and decreased gradually. About the 19th day a rebound may set in; for several types of antigen the increase in the rate of positive cases is insignificant (myocardium, joint capsules) or is altogether lacking (subcutaneous tissue), but for other types (valvular antigen) it is appreciable.

Universal positivity of the sera, *i.e.* cases in which antibody to any type of antigen was found, is not recorded here; it comprised 80·7 per cent. of all sera investigated in the first few days of the disease.

Table I indicates titres of antibody recorded on admission, distributed according to the treatment received before hospitalization. The patients are grouped according to the highest titre of antibody shown, irrespective of the type of antigen responsible for the reaction. It appears that patients who had not been treated at all before hospitalization mostly had titres of 1 : 16 or more, that patients adequately treated showed rather lower titres, and that patients inadequately treated stood roughly in the middle.

By dividing the titres into low (up to 1 : 8 inclusive) and high (from 1 : 16 upwards), as indicated by brackets in Table I, we obtained a six-fold table of contingencies, to ascertain whether the titre level was related to therapy. Evaluation by the χ^2 test has shown that the difference between the predominantly high titres of the untreated or inadequately treated cases and the predominantly low titres of the adequately treated cases is statistically significant at the 2 per cent. level.

Table II shows the percentages of sera which reacted positively to a certain type of antigen and also contained antibody to another type of antigen. For example, of all those sera which in our tests reacted positively to myocardium, 93·1 per cent. also reacted simultaneously to valves, 95·7 per cent. to subcutaneous tissue antigen, and so on. In other words, only 6·9 per cent. of sera reacting with myocardium did not react with valves, only 4·3 per cent. did not react with subcutaneous tissue, and so on. The sera which, while reacting to one type of antigen, did not react to a certain other type, ranged from 4·3 to 27·1 per cent. This means that, although in a given serum one type of antibody is not necessarily accompanied by all other types, in most cases the coexistence of different types of antibody may be assumed as highly probable if one type has been detected.

TABLE I

CORRELATION BETWEEN ANTIBODY TITRE ON ADMISSION AND TREATMENT BEFORE HOSPITALIZATION

Antibody Titre	Treatment before Hospitalization			Total
	None	Inadequate	Adequate	
Negative	2	2	1	10
1 : 4	0 } 3	0 } 2	1 } 5	
1 : 8	1	0	3	
1 : 16	5	3	1	25
1 : 32	8 } 17	2 } 6	1 } 2	
1 : 64	4	1	0	
Total* ..	20	8	7	35*

* Not including three patients transferred from other hospitals.

TABLE II

CORRELATION BETWEEN OCCURRENCE OF AUTO-ANTIBODIES AND OF DIFFERENT ANTIGENS IN SEPARATE BLOOD SAMPLES (PER CENT.)

Sera reacting Positively with	Percentages of Sera also reacting Positively with				
	Myocardium	Valves	Subcutaneous Tissue	Skin	Joint Capsule
Myocardium ..	—	93·1	95·7	88·5	89·0
Valves ..	72·9	—	84·4	77·8	74·4
Subcutaneous Tissue ..	82·2	89·1	—	79·5	79·7
Skin	85·4	93·6	92·6	—	87·1
Joint Capsule	88·3	93·9	93·2	92·8	—

Fig. 2 (overleaf) represents the distribution of patients according to the highest titre of antibody to separate antigens reached at any period. Patients with consistently negative findings for a definite type of antibody ranged from 2·6 per cent. (for antibody to subcutaneous tissue) to 29·8 per cent. (for antibody to joint capsule).

Thus the subcutaneous tissue antigen seems to have been responsible for the highest production of antibody detected, as well as for its highest concentrations (*cf.* the number and rate of titres exceeding 1 : 16); after it come valves, myocardium, skin, and joint capsule in that order. Fig. 2 shows that in some patients a certain type of antibody was always lacking, but there was none who did not harbour in the blood one or other of the antibody types studied, even if these were seen only once

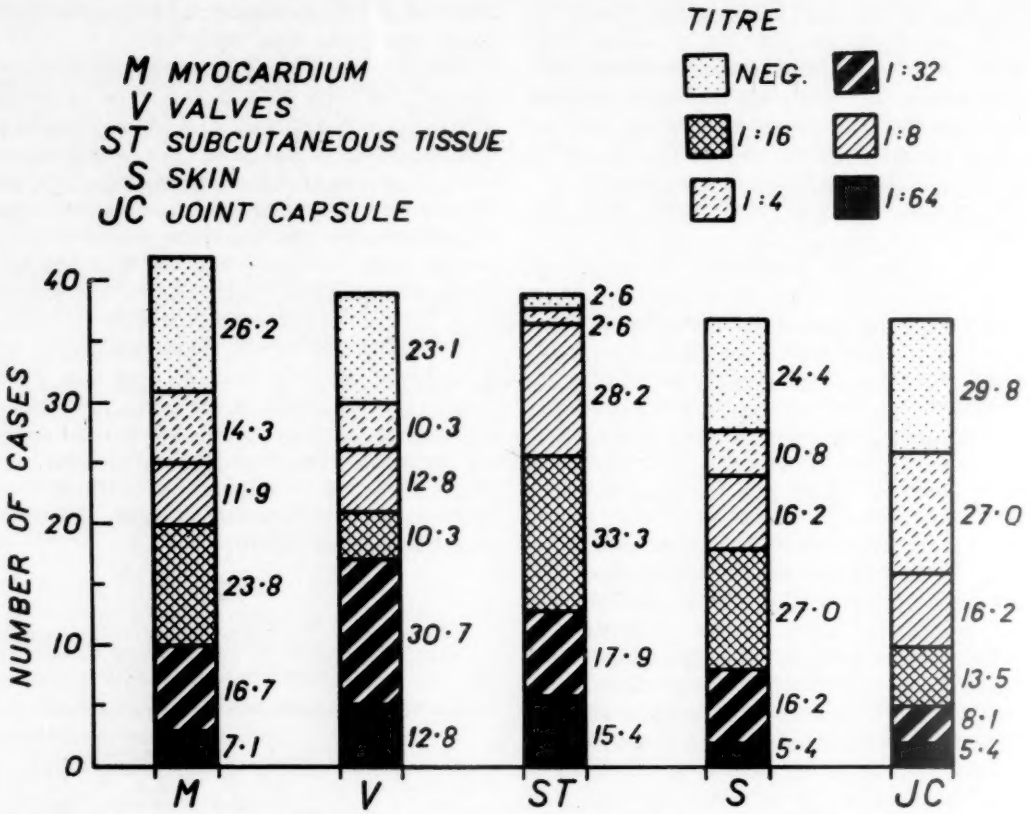


Fig. 2.—Absolute and percentile distribution of patients according to highest antibody titres to separate antigens reached at whatever stage of disease.

Patients hospitalized twice are shown as two cases. For technical reasons a few sera could not be tested for all types of antibody; this accounts for the differing lengths of the columns.

during the period of hospitalization. The seeming incongruity of the values in Fig. 2 with the lower percentages in Fig. 1 is due to the fact that Fig. 1 gives averages of separate short periods, whilst Fig. 2 shows a selection of all the blood samples of each patient.

Fig. 3 (opposite) shows cases investigated from the point of view of presence or absence of clinically demonstrable pathological findings in the heart. In the upper section (A), the cases are ranged according to the highest titre of antibody of any type ascertained at any phase of the disease. Only three cases of all those with heart damage had antibody titres under 1 : 32. Inversely, only four cases lacking clinical signs of carditis had titres of 1 : 32 or more.

The lower section (B) shows only antibodies to myocardium and to valves. Clinically demonstrable heart lesions and high antibody levels tend to parallel each other, though the pattern is not so clear-cut as in Section A, in which all five types of antibody are considered. A possible explanation of this divergence is suggested below.

Table III gives the data for correlating fresh heart lesions with rises in antibody titre caused by recurrence of disease during hospitalization. Only those patients were taken into account who continued to be tested for antibody after the 19th day of hospitalization; this means that the less severe cases which had been discharged from hospital are excluded.

TABLE III
CORRELATION BETWEEN RE-INFECTION, RISE IN ANTIBODY TITRE, AND FRESH HEART DAMAGE AFTER 19TH DAY OF HOSPITALIZATION

Re-infection	Rise in Titre		No Rise in Titre		Total
	With Fresh Heart Damage	Without Fresh Heart Damage	With Fresh Heart Damage	Without Fresh Heart Damage	
Ascertained ..	5	0	0	2	7
Not Ascertained ..	0	3	2	18	23
Total	5	3	2	20	30

Notes: Only substantial rises, *i.e.* from a lower titre (up to 1 : 16) to a higher titre (from 1 : 32 upwards) were considered. Pathological changes in the heart ascertained either by electrocardiogram or by auscultation.

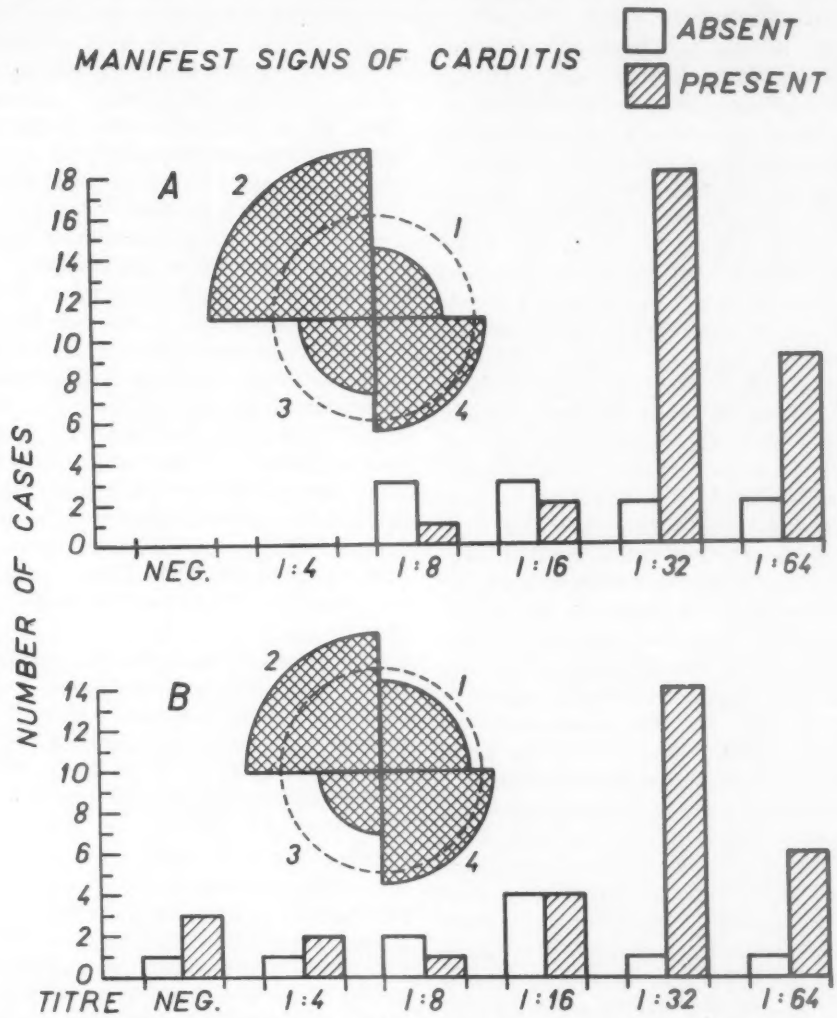


Fig. 3.—Occurrence of auto-antibodies in different titres, related to clinical manifestation of carditis. (A) Antibodies to all five selected types of antigen. (B) Antibodies to heart tissue antigens only.
Quadrant 1: Cases with high antibody titres (above 1 : 16) without signs of carditis.
Quadrant 2: Cases with high titres and signs of carditis.
Quadrant 3: Cases with low titres and signs of carditis.
Quadrant 4: Cases with low titres without signs of carditis.
Dotted Circle: The distribution of these four variants which would be expected if carditis were independent of the antibody titre.

Table III serves to evaluate the significance of the results obtained by the χ^2 test. All three values of χ^2 appear to be significant at the 1 per cent. level. In all the thirty cases which were followed-up, only one had a titre of 1 : 16 on the 20th day of hospitalization; in two patients the titre was 1 : 8 and in one it was 1 : 4, the remaining eighteen being negative.

However, after the 19th day, the titres began to rise (*cf.* also Fig. 1) and in five patients out of seven with clinically ascertainable re-infection they rose rapidly. Simultaneously, these five patients showed fresh heart damage, but no such damage was detected in the two patients whose titres did not rise. Among patients without ascertainable re-infection, eighteen cases showed no substantial rise in titre—though a moderate rise (up to 1 : 8) was recorded in nine of them—neither did their heart condition deteriorate.

Only in two patients did the heart condition become worse without any corresponding substantial rise in the level of antibody. Inversely, a substantial rise was recorded in three patients in whom no heart damage could be detected clinically. No re-infection was found in these five patients.

Discussion

The significance of the auto-antibodies demonstrated in certain diseases has not yet been elucidated, though in some the appearance of antibody is known to precede the clinical manifestations, and there is a striking interdependence of the antibody concentration and organic damage. The aim of the present study was to correlate levels of antitissue antibody with clinical manifestations of rheumatic fever. Some but not all of the observed cases showed a congruity between the serological findings and the clinical pattern, and we therefore adopted statistical methods of evaluation. The explanation of divergent results in particular cases may lie either in the nature of the patient or in the method used.

The occurrence of auto-antibodies to five selected types of tissue in the sera of patients with rheumatic fever was demonstrated by the collodion particle agglutination method. We found that the connective tissues are much less stable in collodion agglutination than the antigenic substances of the parenchymatous organs. Tissues from many cadavers did not give negative results in every control test. Since the tissue extracts used as antigen were not purified, their qualitative and quantitative composition was ignored, but, after weeks and even months of freezing, tissues taken from the same cadaver showed no change in antigenic properties, and this suggests that the common reagent remained the same, so that differences in the results must be due to the properties of the individual sera examined.

Another difficulty lay in the inherent properties of the antibodies themselves. Quite fresh sera, even from healthy subjects, may spontaneously agglutinate tissue antigens in low titres, but the same sera will give negative reactions if left standing for 24 hours. For this reason we never used the sera until 24 hours had elapsed, and the reliability of our findings has therefore not been prejudiced by this factor.

A further precaution was necessitated by the instability of the auto-antibodies, which, as we found in a series of trial experiments, disappear after a week if the sera are not kept at −20° C.; to accelerate freezing, it is even better to cool them to −30 ° C. The storing of sera for long periods at inadequately low temperatures may account for the negative findings reported by some authors (Fischel and Pauli, 1949). The thermolability of antibody makes the standardization of findings very difficult.

In spite of these reservations, the reported findings demonstrate convincingly the interdependence of the occurrence of auto-antibody and the presence of the disease process in the organism. Sera which reacted positively to at least one type of selected antigen made up 80·7 per cent. of the positive findings in the first 4 days of hospitalization. Thus in nearly 20 per cent. of cases no antibody was detected during this period, but it does not follow that this 20 per cent. were always negative, since antibody sometimes shows only in the later course of the disease. In no single case were antibodies not revealed at least once.

On the whole, the fall in the percentage of patients with positive antibodies roughly paralleled the length of time which had elapsed since admission to hospital. Though we could not organize a group of controls who were not adequately treated during hospitalization, we feel entitled to infer a correlation of positive findings with therapy. This tendency is exemplified by Table I which shows the treatment received before hospitalization. In our experience, cases untreated or inadequately treated before admission maintained high antibody levels in hospital longer than other patients. These observations suggest that the change in antibody concentration may be used as an index of adequacy of therapy.

From the discrepancies between the incidence of positive reactions by the same blood sample to different types of antigen (Table II) it follows that the sera of patients with rheumatic fever contain not one type of antibody only, but a whole spectrum of antibodies directed against different components of the examined tissues. In separate samples we observed every possible combination of reactions to the antigens employed, high titres of antibody to one antigen and negative results to others. Several patients responded differently to the same type of antigen on different days. This phenomenon cannot be explained away simply by assuming quantitative differences in the single components of tissue antigens of different types. It seems more likely that different types of tissue differ qualitatively in their antigenic composition (Pressman, Sherman, and Korngold, 1951). Biochemical fractionation of the tissues is a necessary preliminary to the elucidation of this problem.

In eight cases out of thirty a rise in antibody production occurred after the 19th day of hospitalization. Re-infection contributed to this rise in five of the eight cases (Table III).

The levels of antitissue auto-antibody in each of the investigated patients were correlated with laboratory and clinical tests of disease activity, especially the Weltman reaction and the erythrocyte sedimentation rate. To some extent these results corresponded, but the significance of the presence and amount of antibody seems to differ from that of the other reactions. It seems, too, that auto-

antibodies persist longer than other accepted criteria of disease activity. Histological findings of fresh Aschoff bodies in myocardia showing no clinical signs of disease prove that sub-clinical rheumatic activity persists in many convalescents. It would be useful to make a special study comparing these findings with the incidence of auto-antibodies. Until this aspect of the problem is examined, we may assume that the presence of auto-antibodies is a rough index of disease activity, latent or otherwise.

In order to examine the relationship between the incidence of antibodies and various tissue lesions, we investigated five different types of tissue on the assumption that different separate organs might be independently involved. The relationship between high titre levels of auto-antibody and clinical heart damage was found to be statistically significant, cases showing titres of 1 : 32 or more being extremely likely to show clinically demonstrable myocardial or valvular damage. The dependence of organic lesions on the presence of antibodies in the serum is, however, not absolute, for the following reasons:

(1) A certain type of antibody may have been present in high concentration in the patient's serum before admission, but may have already been absorbed by the tissues (Sarre and Wirtz, 1939; Pressman, 1951) and be, therefore, no longer demonstrable in the blood. This localization of the antibody in the appropriate organ takes place very rapidly (Pressman, Eisen, and Fitzgerald, 1950). This observation is corroborated by our own experience: one patient who showed a titre of 1 : 32 on admission was subsequently persistently negative, but the carditis resisted every form of therapy, and at necropsy, fresh myocardial and valvular lesions were found.

(2) Antibody may damage organs without producing clinical signs of involvement (Clark and Anderson, 1955).

(3) Salicylate therapy may cause a sero-negative reaction (Derick, Hitchcock, and Swift, 1928; Wagner and Zavazal, 1955) without presenting pathological changes in the heart tissue.

(4) Collodion agglutination may not intercept every type of antibody, and incomplete antibodies of various descriptions may thus escape detection.

The interdependence of the level of auto-antibody in the blood and the tissue lesions (Fig. 3 and Table III), relative though it is, seems to indicate that antibody in the blood must reach a certain concentration before it is able to penetrate the tissue and accumulate there in sufficient amounts to provoke changes that are clinically demonstrable. Theoretically, a reverse order of cause and effect can be envisaged. Antibody may appear in consequence of a pathological process which may already have taken its course in the tissue. The appearance of antibody might thus be a sort of secondary index and not the cause of the pathological process (Vorlaender and others, 1954). In another series of tests (Wagner and Šeba, 1956), one of us observed a case of pemphigus in which a high concentration of antibody was detected in the patient's serum and bullae appeared on the skin on the following day, simultaneously with the shifting of auto-antibody from the blood into the blister fluid. This observation, like one previously made by Lippman and others (1950), as well as the analogy with immuno-haematological processes, supports the hypothesis of the pathogenic effects of auto-antibody, though these hitherto fragmentary experiences cannot be extended to the rheumatic diseases in general.

Fig. 3 shows that patients with heart lesions may present low antibody titres to heart tissue antigens. A comparison of Fig. 3A with Fig. 3B shows that though the titre of antibody to subcutaneous tissue and skin tissue may be high, the titre to heart tissue may be low or even absent. At first sight these findings seem paradoxical, but perhaps these specific anti-heart tissue antibodies are immediately absorbed by the heart tissues in which their high concentration rapidly causes lesions; thus these specific heart antibodies disappear from the blood whilst other types of antibody remain.

Summary

The collodion agglutination method was applied to investigate anti-organal antibodies to antigens from human myocardium, valves, subcutaneous tissue, skin, and joint capsule. The examinations were carried out with sera from 38 hospital patients with rheumatic fever. The serological results were compared with the results of other laboratory and clinical examinations. The greatest attention was paid to the correlation of antibody with damage to myocardium and valves.

Antibody was found at least once in the blood of each patient, but the incidence of antibodies to single antigens ranged from 70·2 per cent. (to joint capsule antigen) to 97·4 per cent. (to subcutaneous tissue antigen). During the first week of hospitalization 80·7 per cent. of patients were found to have antibody to at least one type of antigen in the blood.

The findings of anti-organal antibodies were compared with the therapy received before hospitalization. Patients who had been inadequately treated or not treated at all showed a higher incidence and higher levels of antibody. The interdependence between antibody findings and signs of heart damage was statistically significant, whether all five types of antibody or only the anti-myocardial and anti-valvular types were taken into account. Re-infection in the course of the disease made the titre rise in a statistically significant manner. A

certain parallelism was seen between the antibody concentration and the activity of the rheumatoid process as measured by the erythrocyte sedimentation rate and Weltman reaction. On the other hand, antibody was not found at all in the very numerous control group of healthy subjects (blood donors and sanitary personnel).

REFERENCES

Brokman, H., Brill, J., and Frendzel, J. (1937). *Klin. Wschr.*, **16**, 502.
Cavelti, P. A. (1945). *Proc. Soc. exp. Biol. (N.Y.)*, **60**, 379.
—— (1947). *J. Immunol.*, **57**, 141.
Clark, R. M., and Anderson, W. (1955). *Amer. J. Path.*, **31**, 809.
Coburn, A. F., and Pauli, R. H. (1939). *J. exp. Med.*, **69**, 143.
Derick, C. L., Hitchcock, C. H., and Swift, H. F. (1928). *J. clin. Invest.*, **5**, 427.
Fischel, E. E., and Pauli, R. H. (1949). *J. exp. Med.*, **89**, 669.
Humphrey, J. H. (1948). *J. Path. Bact.*, **60**, 211.
Klujeva and Bobritzkaja (1934). *Acta rheumatol. (Amst.)*, **6**, No. 20-21, Appendix, p. 4.
Lange, K., Gold, M. M. A., Weiner, D., and Simon, V. (1949). *J. clin. Invest.*, **28**, 50.
Lansbury, J., Crosby, W. R., and Bello, C. T. (1950). *Amer. J. med. Sci.*, **220**, 414.
Lippman, R. W., Cameron, G., and Campbell, D. H. (1950). *Proc. nat. Acad. Sci. (Wash.)*, **36**, 576.
McFarland, J. (1907). *J. Amer. med. Ass.*, **49**, 1176.
McKee, K. T., and Swineford, O. (1951). *Annals of the Rheumatic Diseases*, **10**, 116.
Osler, A. G., Hardy, P. H., and Sharp, J. T. (1954). *Amer. J. Syph.*, **38**, 554.
Peck, J. L., and Thomas, L. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, **69**, 451.
Pressman, D., Eisen, H. N., and Fitzgerald, P. J. (1950). *J. Immunol.*, **64**, 281.
—— and Sherman, B. (1951). *Ibid.*, **67**, 21.
——, ——, and Korngold, L. (1951). *Ibid.*, **67**, 493.
Ramsdell, S. G., and Davidsohn, I. (1930). *Ibid.*, **18**, 473.
Rejholec, V., Vančura, A., Wagner, V., and Mandlikova, Z. (1952). *Sborn. lék.*, **54**, 195.
—— and Wagner, V. (1955). *Experientia*, **11**, 278.
——, ——, and Mandlikova, Z. (1952). *Sborn. lék.*, **54**, 217.
Sarre, H., and Wirtz, H. (1939). *Klin. Wschr.*, **18**, 1548.
Steffen, C. (1954a). *Wien. Z. inn. Med.*, **35**, 422.
—— (1954b). *Klin. Wschr.*, **33**, 134.
—— and Rosak, M. (1955). *Wien. Z. inn. Med.*, **36**, 40.
—— and Schindler, H. (1955). *Schweiz. Z. allg. Path. Bakt.*, **18**, 287.
Vorlaender, K. O. (1952). *Z. ges. exp. Med.*, **120**, 9.
——, Fitting, W., and Blankenheim, H. (1954). *Z. Rheumaforsch.*, **13**, 276.
Wagner, V. (1954). *Schweiz. Z. allg. Path. Bakt.*, **17**, 94.
—— and Seba, G. (1956). *Dermatologica (Basel)*, **112**, 25.
—— and Zavazal, V. (1955). *Z. Immunforsch.*, **112**, 260.
Wedum, A. G., and Wedum, B. G. (1946). *Proc. Soc. exp. Biol. (N.Y.)*, **61**, 432.
Weintraud, W. (1913). *Berl. klin. Wschr.*, **50**, 1381.

Réaction par des anticorps contre les antigenes des tissus au cours du rhumatisme articulaire aigu

RÉSUMÉ

La méthode d'agglutination au collodion fut employée pour rechercher les anticorps spécifiques aux antigènes provenant du myocarde, des valvules, du tissu sous-cutané, de la peau et de la capsule articulaire humains. Les examens furent effectués avec des sérums provenant de 38 malades hospitalisés, atteints de rhumatisme articulaire aigu. Les résultats sérologiques furent comparés avec les résultats d'autres examens cliniques et de laboratoire. On prêta la plus grande attention à la relation entre l'anticorps et le dommage myocardique et valvulaire.

Un anticorps fut trouvé au moins une fois dans le sang de chaque malade, mais le rapport des anticorps aux particuliers antigènes était compris entre 70,2% (pour l'antigène de la capsule articulaire) et 97,4% (pour l'antigène du tissu souscutané). Durant la première semaine d'hospitalisation 80,7% de malades se révélèrent avoir des anticorps contre au moins un type d'antigène du sang.

Les découvertes d'anticorps anti-organe furent considérées en relation avec le traitement avant l'hospitalisation. Les malades qui avaient été soignés insuffisamment ou pas du tout, avaient des anticorps plus souvent et en quantité plus élevée. L'interdependance entre les découvertes d'anticorps et les signes de lésion cardiaque était statistiquement significative, soit que l'on considérât les cinq types d'anticorps ou seulement les types antimyocardique et antivalvulaire. La re-infection durant la maladie faisait monter le titre d'une façon statistiquement significative. Un certain parallèle se montrait entre le taux d'anticorps et l'activité du processus rhumatismal, mésurée par la vitesse de sédimentation érythrocytaire et la réaction de Weltman. D'autre part, on n'a pas trouvé d'anticorps du tout parmi les très nombreux témoins (donneurs de sang et personnel sanitaire).

Reacción por anticuerpos contra antigenos de los teïidos en el curso del reumatismo poliarticular agudo

SUMARIO

Con la ayuda del método de aglutinación al colodión se buscaron los anticuerpos específicos a los antígenos del miocardio, de las valvulas, del tejido subcutáneo, de la piel y de la cápsula articular humanos. Se investigaron sueros de 38 enfermos hospitalizados afectos de reumatismo poliarticular agudo. Los resultados serológicos fueron comparados a otros datos clínicos y de laboratorio. La correlación entre los anticuerpos y las lesiones del miocardio y de las valvulas fué considerada con un cuidado particular.

Un anticuerpo fué encontrado al menos una vez en la sangre de cada enfermo, pero la incidencia de los anticuerpos respecto a los antigenos particulares variaba del 70,2% (para el antígeno de la capsula articular) al 97,4% (para el antígeno del rejido subcutaneo). Durante la primera semana de hospitalización el 80,7% de los enfermos reveló la presencia de anticuerpos contra al menos un tipo de antígeno en la sangre.

Los hallazgos de anticuerpos "anti-organos" particulares fueron considerados en relación con el tratamiento recibido antes de la hospitalizacion. Con un tratamiento anterior insuficiente o ausente, los anticuerpos encontráronse más a menudo y en mayor cantidad. La interdependencia entre el hallazgo de anticuerpos y la existencia de lesiones cardiacas fué estadisticamente significativa, tanto respecto a los cinco tipos de anticuerpos como en relación al antimiocárdico y antivalvular solos. La reinfección en el curso de la enfermedad hacía subir las cifras de manera estadisticamente significativa. Hubo un cierto paralelismo entre las cifras de anticuerpos y la actividad del proceso reumático, medida por la velocidad de la sedimentación eritrocitaria y por la reacción de Weltman. En cambio, no se encontraron anticuerpos algunos en los muy numerosos testigos (dadores de sangre y personal sanitarioy)

BOOK REVIEWS

Der Rheumatismus. Edited by R. Hopmann. 1956. Pp. 99, 29 figs. Georg Thieme Verlag, Stuttgart. (D.M. 16.50; 28*s*.)

With the help of his colleagues at the University of Cologne, Professor Hopmann has produced a volume of about 100 pages into which he has compressed the views of a pathologist, bacteriologist, paediatrician, orthopaedic surgeon, etc. This has widened the horizon but has also given scope for a number of points of view which are sometimes difficult to reconcile. Nevertheless, it is apparent that the adherents of the theory of focal sepsis have received little, if any, opposition. It is pleasant to record that the names of British workers figure in the text and that in describing pain-distribution pride of place has been given to diagrams by Lewis and Kellgren, and by Copeman. The reader is introduced to the mysteries of C-reactive protein and the more recent work in the field of rheumatology, and for the middle-aged rheumatologist, who believes in the Byronic dictum that "the days of our youth are the days of our glory", the Editor, perhaps without realizing it, has provided a nostalgic classification of the rheumatic diseases in which "Sciatica" comes under the heading of "Neuralgias" and "Muscular Rheumatism" is placed in a category of its own.

Paper, print, *x*-ray photographs, etc., are all of excellent quality; the references provided at the end of each chapter bear an international character.

DAVID PREISKEL.

Joint Ligament Relaxation treated by Fibro-Osseous Proliferation. By George Stuart Hackett. 1956. Pp. xiv+917, illus. Blackwell Scientific Publications, Oxford; Thomas, Springfield, Ill. (36*s*.)

In this book the author describes his approach to the problem of chronic low backache and gives details of his method of treatment. Dr. Hackett believes that most cases of low backache, and of pain referred into the legs from the back, are due to "relaxation" of specific ligaments such as the ilio-lumbar and sacro-iliac: relaxation, following defective repair at the fibro-osseous junction after injury, allows abnormal lengthening of the ligament under tension, producing pain from stimulation of nerve fibres within the ligament. A similar process is held to account for chronic pain affecting other joints such as the wrist and ankle. Methods for localizing the origin of the pain are described, together with the technique of treatment by injection of a sclerosing or "proliferating" solution.

Low backache is certainly common, and often enough it is difficult to make a precise diagnosis, while treatment may be prolonged and disappointing. Protruded intervertebral disk and spondylosis have replaced fibrositis as the most frequently named cause, but there has been no remarkable advance in treatment. But, while Dr. Hackett may justifiably condemn the ill-considered laminectomy or spinal fusion, one feels that in his enthusiasm for his own methods, his attitude to other ideas has become, perhaps, less than objective; not everyone would agree that disk lesions should only be diagnosed if there are neurological signs of root compression, while hyperextension in such cases ought, by reducing tension on the posterior spinal ligaments, to relieve pain if the author's views are accepted, whereas in fact it usually accentuates it. It is not easy to understand why injection of a "proliferating solution" should cure tennis-elbow, when hydrocortisone, which presumably acts in quite the opposite way, will also do so.

Nevertheless, it is recognized that pain can arise from ligaments and may be referred to distant areas, and such a mechanism as Dr. Hackett describes may well account for the pain of chronic "sprains" and of a number of cases of backache: if his method works it will surely be welcomed by those patients who are too often forced to resort to those practitioners whom Dr. Hackett succinctly describes as "disk jockeys and bone masons".

A. J. POPERT.

OBITUARY

MATHIEU-PIERRE WEIL

Dr. Mathieu-Pierre Weil, who died in Paris in March, 1956, stood at the cradle of the "Ligue Internationale contre le Rhumatisme" with Dr. Fortescue Fox, Dr. Pemberton, Dr. van Breemen, and Dr. Ginsburg. He had been Vice-President of the French National League and after the second world war was chosen as the first President of the newly-founded Ligue Européenne.

Of his scientific achievements we call attention especially to his work on gout and on sacro-ileitis in ankylosing spondylitis.

We honour and remember him as one of the pioneers in modern rheumatology.

J. GOSLINGS.

Ann. rheum. Dis. (1956), **15**, 374.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1956

The Annual Meeting of the American Rheumatism Association was held at Chicago, Illinois, on June 8 and 9, 1956, under the presidency of Dr. Charles L. Short of Boston. Abstracts of 30 papers and the discussions thereon are printed below. One session was arranged in conjunction with the American Council on Rheumatic Fever and Congenital Heart Disease. Panel Discussions were held on "Gout" (Moderator: Dr. A. Gutman) and on "A Teaching Collection of Lantern Slides illustrating the Pathology of Arthritis and Rheumatism", the work of a Sub-committee of the Arthritis and Rheumatism Foundation (Moderator: Dr. Currier McEwen). A report on "Proposed Diagnostic Criteria for Rheumatoid Arthritis" was presented by the Committee on Diagnostic Criteria (Chairman: Dr. Marian W. Ropes).

Presidential Address

BY

CHARLES L. SHORT

President of the American Rheumatism Association, 1955-56

The presidential addresses delivered before this association have usually dealt with a clinical or scientific subject of special interest to the speaker at the time or with broad and general aspects of teaching and research in the rheumatic diseases. Only a few have considered in some detail the activities and aims of your association —subjects with which I have been intimately concerned during the past year, and which I wish to discuss this afternoon in a brief and necessarily incomplete form.

Just 10 years ago, in May, 1946, the American Rheumatism Association assembled in New York for what was aptly termed a Reunion Meeting. During the war years, no meetings had been held and no new members added. The affairs of the society had been in the custodial care of the Officers and Executive Committee while the greater part of the membership was scattered far and wide in the armed forces. In his presidential address at this meeting, Dr. W. Paul Holbrook, took the opportunity to present what he called major goals or challenging opportunities for accomplishment by the association and its membership. These goals were four in number. While successfully achieved in part, they bear repetition and re-emphasis a decade later, along with additional comments provoked by the changing outlook in which we have all shared on the still elusive search for the cause and cure of the rheumatic diseases.

I should like to mention one goal first, perhaps because it has been achieved so magnificently and I am sure beyond the expectation of the membership 10 years ago. This is what Dr. Holbrook modestly called a strengthening of the work in public relations, with the eventual development of a fund-raising organization. Within 2 years the Arthritis and Rheumatism Foundation was established. In another 2 years, by the combined efforts of the Foundation and our own Association, the National Institute working in the field of metabolic diseases was expanded to include the field of rheumatism and funds were appropriated by Congress to carry on this augmented work. We are now blessed with the happy co-operation of professional, voluntary, and governmental groups, all concerned with a common objective, the alleviation and eventual prevention of a group of chronic disabling diseases.

It is unnecessary to list in detail to this audience the contributions made by the Arthritis and Rheumatism Foundation, both nationally and locally, to an improved outlook for the rheumatic patient, not only at this time, by the education of those concerned with his care, but also in the future, by the financing of clinical and basic research. To quote just two figures, the amount expended for such investigations in the United States has increased from $300,000 yearly in 1948 to $3,000,000 in 1955. No statistical tests of significance are necessary to assume an association between this increase and the operations of the Arthritis and Rheumatism Foundation and the National Institute for Arthritis and Metabolic Diseases.

A second major goal set 10 years ago was the education of physicians in the basic treatment of arthritis. The last 6 years' experience with suppressive agents, valuable as they are in selected cases and as research tools, has failed to diminish the importance of measures generally believed to be helpful in the management of a disease like rheumatoid arthritis. I say "generally believed to be helpful", because the value of rest, salicylates, simple forms of physical therapy, non-operative orthopaedic measures, and above all the study and treatment of the patient as a human being, has yet to be established by

controlled therapeutic studies. Nevertheless, few of us would wish to discard such measures, whether or not suppressive agents are also used. To supply the practitioner with the knowledge and will to prescribe these methods in a specific and detailed fashion is no easier task to-day than it was 10 years ago. In addition, we have the obligation of pointing out the proper indications for suppressive treatment, along with warnings against its injudicious or unwarranted use. Certainly these objects have begun to appear within closer reach through the educational programme of the Arthritis and Rheumatism Foundation as related to the practitioner. The *Bulletin on Rheumatic Disease*, the *Primer*, and the *Rheumatism Review*, while created by our member, could never have received their present wide distribution to the medical profession, nor could our exhibits have been financed without assistance from the Arthritis and Rheumatism Foundation. Valuable as these methods are, our personal contact with the practitioner should provide opportunity for more vivid and effective forms of instruction. These include not only talks at society and staff meetings and the careful teaching of trainees and of physicians assisting in arthritis clinics, but especially our teaching in regard to diagnosis and patient management as consultants. If the referring physician is given a detailed, conscientiously prepared outline of the problems presented by an individual patient and their best solution, he should gradually but surely be able to apply what he learns to other cases of rheumatic disease encountered in his practice.

In 1946, only one local rheumatism society was affiliated with the American Rheumatism Association. This was the New York Rheumatism Association, which was host to the parent society at the Reunion Meeting. The third major goal was the organization of affiliated societies "in every community that can support one". A substantial growth in their number has taken place since then, the present total being 25. Six have been added in the last year, largely through the effective efforts of the Committee on Affiliation with Local Societies. But since there are still 25 states without such a society, the challenge still lies before us.

The fourth major goal was "a wise and progressive enlargement of membership". As shown in Fig. 1, the membership has steadily increased, with a recent spurt due to the personal efforts of our last year's president. We still need more new members representing the widely varying interests of those now concerned with the study and treatment of rheumatic disease. The Table brings out the latter point; the first column lists those whose purpose is to help the rheumatic patient more effectively and the second those primarily concerned with the advancement of knowledge in this field.

Most rheumatologists, or rather most internists with a major or substantial interest in musculoskeletal disease, are already among our members. We must be on the look-out, however, for additional members from this group, whether younger or older, once it is clear that their interests lie in this direction.

Since rheumatic disease frequently contributes to disability in our aging population and may be incapacitating or even fatal in childhood, geriatrists and pediatricians, who are fundamentally internists, should be brought into our membership.

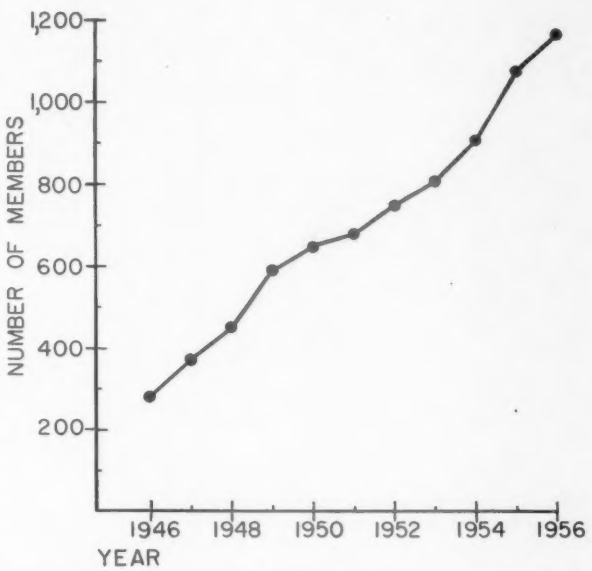


Fig. 1.—Membership of the American Rheumatism Association from 1946 to 1956.

The question may be raised whether the general practitioner or generalist belongs in the society. I feel that a certain number do, along with internists for whom rheumatism represents only one facet of their practice. Such individuals can learn and be stimulated by attendance at our meetings, and can also contribute to them by their clinical observations of early and atypical disease and their unique privilege of following certain patients through a lifetime of practice.

I include the radiologist because the clinical members of our society rely on his skill so often in their diagnoses, but, as far as I can recall, it is some time since a distinctly radiological communication has been read at one of our meetings.

Orthopaedists are among the founding fathers of the Society and, in addition to their contributions to recon-

TABLE

CLASSIFICATION OF PHYSICIANS AND INVESTIGATORS ENGAGED IN THE STUDY AND TREATMENT OF THE RHEUMATIC DISEASES

"Rheumatologist"	Clinical Investigator
Internist	Epidemiologist
Pediatrician	Biostatistician
Geriatrist	Fundamental Investigator
Generalist	Biologist
Radiologist	Biochemist
Orthopedist	Histochemist
Physiatrist	Biophysicist
Psychiatrist	Embryologist
Military Surgeon	Bacteriologist
Industrial Physician	Immunologist
Pharmaceutical Physician	Pathologist
	Pharmacologist

structive surgery, are often the first to see a patient with joint disease. For this reason alone, a greater representation of orthopaedic surgeons in our membership is desirable, along with a wider dissemination of informative articles on rheumatic disease in orthopaedic publications. A healthy sign of a closer relationship is the recent appointment by the American Academy of Orthopaedic Surgeons and the American Rheumatism Association of a Joint Committee on the nomenclature of painful shoulder syndromes.

The important place of physical therapy and rehabilitation in the management of the arthritic is as obvious as the physiatrist's need to keep abreast of advances in articular disease.

The psychiatrist is also concerned with the elucidation and well-rounded treatment of connective tissue diseases. Although the methods by which psychogenic factors may influence the host are not yet clear, the psychiatrist's help is needed to render our understanding of the patient as complete as possible.

The military surgeon and the industrial physician are included because the rheumatic diseases comprise a large share of disability and loss of manpower both in the armed services and in industry. They have an unequalled opportunity to obtain data on disease frequency and to organize large-scale programmes for disease prevention.

The pharmaceutical physician, furnishes liaison between the companies engaged in the development and distribution of new therapeutic agents and the clinical investigator and practitioner. The undesirable and premature publicizing of new remedies has been for some time a matter of concern to our members. Let us take more pharmaceutical physicians into the fold, in order that they may learn of the problems in patient relationships created by such publicizing and become better acquainted with the meaning of a controlled therapeutic trial.

To turn to the second list in the Table, the clinical investigator has made up the backbone of our society from its inception. In most instances, a member thus classified has undertaken the care and treatment of other rheumatic patients besides those who contribute their body fluids and tissue to his studies or supply the opportunity to observe the natural history of their disease. I have not attempted to classify clinical investigators into sub-groups. The broad field of rheumatism is now being approached from many directions, with the employment of multiple chemical, physiological, pathological, and statistical techniques in addition to accurate clinical observation.

I have listed the epidemiologist separately because of the paucity of even limited epidemiological studies in the rheumatic diseases. For example, information in regard to the natural history of a disease like rheumatoid arthritis is now based on hospital or clinic patients and can only be surmised in the population at large.

More biostatisticians should also be included; they are needed by fundamental and clinical investigators alike for assistance in the design and interpretation of experiments and therapeutic trials and in the establishment of quantitative methods for the recording and evaluation of clinical phenomena.

The remaining categories are listed under the heading "Fundamental Investigator". There are no fixed lines of demarcation between fundamental and clinical studies and both will continue to benefit from a whole-hearted interchange of ideas and methodology. However, the concept of the connective tissue diseases, now existent for over 20 years, has led directly to an attempt to characterize this tissue in regard to structure, composition, reactivity, and especially physiology, so that, as the normal is defined, we can better interpret the alterations produced by disease. This approach requires the use of modern analytical methods, including those developed by physicists and applied by biologists.

I have used the term biologist in the list to denote that the investigator in this field need not be restricted to a single discipline. It has been suggested, for example, that the embryological approach deserves more attention and that information about the development of the connective tissues in an embryonic stage may be important in the study of both normal and abnormal healing, regeneration and growth. It may be hoped that this society will continue to attract to its membership the connective tissue biologist, who surely looks for clinical corroboration in many of his problems and desires to see his work eventually reach useful application.

Most of the papers on our early programme of a fundamental nature were concerned with bacteriology and immunology, and to-day workers in these fields continue to contribute an important part of the basic exploratory work in rheumatic disease.

The pathologist not only remains indispensable as a partner in clinical and fundamental investigation but can also furnish important clues to the origins and mechanisms of disease by the methods of classical histology.

The pharmacologist is finally listed since his contributions may become greater as the number of agents suppressing connective tissue inflammation increases.

To repeat the original premise, a carefully selected increase in membership is one of our major objectives. May this incomplete check-list prove useful in the recruiting by each one of you of new members who can contribute by their special talents to the aims of the association and in turn receive assistance in the successful accomplishment of their clinical or scientific endeavours.

I should finally like to discuss briefly the nature and content of our scientific programmes (Fig. 2, opposite). I have divided the papers given at the annual meetings (invited speakers being excluded) into three categories:

The topmost division refers to fundamental studies; the nature of connective tissue and its chemical or physical alterations in health and disease; fundamental aspects of infection and immunity in relation to rheumatic disease; purely laboratory research including experimental arthritis.

The middle division is made up of clinical investigation, and embraces epidemiological studies and controlled therapeutic trials as well as the use of laboratory techniques.

The lowest division, not necessarily the least important, includes purely clinical aspects of connective tissue disease.

Each whole block represents an era in the life of the Association, the first encompassing the pre-war years and the next two sharing the 11 years since meetings were resumed after the war. For comparison, an analysis of the papers presented at the two Interim Sessions is shown in the fourth block. In each block, the mean unweighted percentages are given of papers in the three categories.

No startling conclusions are to be drawn from this figure, which I shall interpret with caution since it was not prepared with the aid of a biostatician. Papers on

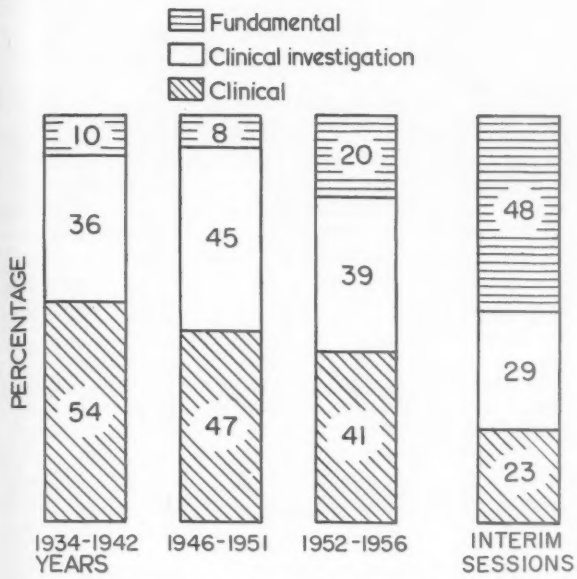


Fig. 2.—Papers presented at the Annual Meetings and at the 1954 and 1955 Interim Sessions of the American Rheumatism Association.

clinical investigation have continued to make up about 40 per cent. of those presented, while the proportion of purely clinical papers has slightly decreased and those devoted to fundamental studies have increased. There is an obvious bias in the percentages for the Interim Sessions, in that members and research fellows who are not yet members have thus far been encouraged to present investigations of a basic nature at this meeting. It will be interesting to see whether this division of the Interim Session papers persists in future years. I am willing to predict that the programmes of the Annual Meeting and of the Interim Session will eventually come to resemble each other more closely.

The criticism has been not infrequently heard from some of our clinical members in recent years that our meetings are too scientific, the fundamental investigators, either more tolerant or less articulate, having apparently failed to bring up the converse. A psychiatric interpretation of this situation has been suggested: that clinicians like myself experience a feeling of inferiority as the complexities of modern biophysical and biochemical techniques are revealed. That thus far clinical studies have failed to disclose specific leads as to the aetiology of the connective tissue diseases hardly seems the main reason for the fundamental approach. It is rather that a better understanding of disease mechanisms and treatment can result only from a greatly extended knowledge of the anatomy, physiology, and reactions caused by disease of the tissue chiefly involved. More important, both fundamental and clinical studies have benefited greatly from the exchange of ideas and constantly stimulate each other. It is highly possible that the next great advance in rheumatism may be derived from careful clinical observation.

In conclusion, it is my hope that the membership of the American Rheumatism Association will become even more representative of all those engaged in the study and treatment of the rheumatic diseases, and that the programme will contain substantial but necessarily varying proportions of papers dealing with purely clinical subjects, clinical investigation, and fundamental research. Little would be gained and much lost by any division of the society or of its meetings into clinical and laboratory units. As the concept of the connective tissue diseases has provided a unifying influence on research in rheumatic conditions, so may the American Rheumatism Association continue as the chief integrating force in the United States towards their eventual solution.

Influence of Growth on Some Connective Tissue Components extracted in Neutral Salt Solutions. By JEROME GROSS, *Boston, Mass.*

Much has been learned concerning the mechanism *in vitro* fibril formation in solutions of purified collagen. Attempts to relate this knowledge to fibrogenesis *in vivo* have led towards efforts to identify precursors of collagen, factors regulating fibril formation, and components responsible for some physical chemical properties of connective tissue.

Cold neutral salt extracts of fresh corium from growing guinea-pigs are very viscous. Electrophoretic diagrams of such extracts, in addition to showing patterns qualitatively similar to that of serum, reveal also a high hypersharp slow-moving boundary in the γ-globulin fraction. An analogous additional peak is found in the ultracentrifuge pattern.

This boundary proves to represent a dissolved collagen fraction in concentrations up to 0·3 per cent. which can be precipitated as a gel of striated fibrils by warming to 37° C. The viscosity of extracts was almost completely destroyed by collagenase in 15 min. at room temperature and was essentially unaffected by trypsin or hyaluronidase at the appropriate pH. Restriction of growth rate by diet was paralleled by reduction in viscosity of the extracts, which in turn was a nearly linear function of the hydroxyproline content. Static weight for 10 days resulted in a 5-10-fold drop in relative viscosity paralleled by an equal fall in hydroxyproline. Starvation for 2 days after a period of rapid growth resulted in a 5-fold decrease in viscosity and hydroxyproline content. Much smaller decreases in tyrosine (non-collagenous protein) and bound hexose unrelated to viscosity were noted. No significant changes were noted in content of hexosamine or uronic acid. Ultracentrifuge and electrophoretic patterns reflect these changes mainly in the collagen peak.

Similar studies on scorbutic tissues now in progress are complicated by this superimposed growth effect. It is concluded that the collagen extracted by neutral salt solutions is derived from the extrafibrillar ground substance and may play an important role in the physiochemical properties of the connective tissue.

Discussion.—DR. MORRIS ZIFF (*New York, N.Y.*): Have you used starved animals to see whether there is any relationship between the percentage of the soluble extract and the concentration of fibroblasts in the tissue?

DR. GROSS: We are waiting for our histological preparations to be completed. The chemical studies have moved faster.

Influence of Beta-Aminopropionitrile on Developing Connective Tissue. By D. MURRAY ANGEVINE, JOHN E. MIELKE, and JOSEPH J. LALIGH, *Madison, Wis.*

Synthetic beta-aminopropionitrile (BAPN) when fed to rats may modify the developments of bone, cartilage, and connective tissue. To study the influence of this substance on developing connective tissue, croton oil pouches were produced in rats and the walls of such pouches from test and control animals were examined both histologically and chemically.

33 Sprague Dawley rats, weighing 161 to 187 g. were divided into groups of twelve control rats and 21 test rats which received between 0·15 and 0·20 ml. BAPN per 100 ml. drinking water per day. After 6, 12, and 18 days, rats from each group were killed and sections taken from the pouches for microscopic study. The remaining pouch tissue was used for chemical studies. The net weight of the test pouches was less than the corresponding control pouches, their exterior was irregular and indistinct from the surrounding areolar tissue, and in contrast to the controls fifteen of the test pouches had collapsed by the end of 18 days.

Microscopically the fibroblasts from the test pouches showed retarded maturation. The connective tissue cells were still rounded and vesicular after 18 days and, in addition, the collagen fibres of the test pouches did not show the usual progression in development or organization with respect to time as did the collagen fibres from the control pouches.

The connective tissue was analysed for hexosamine and hydroxyproline. The values for hexosamine from the test pouches were comparable to those observed in the controls. There was a definite decrease in the hydroxyproline in the test rats which agreed with the microscopic observation of delayed collagen synthesis on microscopic examination.

Biosynthesis of Hyaluronic Acid by Group-A Streptococci. By ALBERT DORFMAN and J. ANTHONY CIFONELLI, *Chicago, Ill.* (By invitation.)

Previous studies from this laboratory have shown that, with appropriate isotopic precursors, the mechanism of biosynthesis of hyaluronic acid can be studied utilizing a strain of Group-A streptococcus. These studies established the precursors of the fourteen different carbon atoms of the disaccharide-repeating unit of hyaluronic acid. The recent discovery of a series of uridine nucleotides which contain the monosaccharide portions of hyaluronic acid and the demonstration that uridine diphosphoglucose is involved in the synthesis of sucrose and trehalose have suggested that uridine nucleotides may be involved in the biosynthesis of mucopolysaccharides. Glaser and Brown (1955) have reported the incorporation of radioactivity in low molecular weight hyaluronic acid as a result of the action of an enzyme preparation derived from Rous sarcoma on labelled uridine diphospho N-acetylglucosamine. Similar experiments in this laboratory utilizing streptococcal extracts have led to the incorporation of only small amounts of radioactivity.

A study has been undertaken to attempt to identify possible intermediates in the synthesis of hyaluronic acid utilizing extracts of streptococci. Uridine diphospho-N-acetylglucosamine and uridine diphosphoglucuronic acid have been identified in these extracts. An additional uridine nucleotide containing an unidentified amino sugar has also been demonstrated. This compound appears to be identical with one of the nucleotides previously isolated by Park (1952) from penicillin-treated staphylococci.

Discussion.—DR. R. J. WINZLER (*Chicago, Ill.*): I should like to inquire whether Dr. Dorfman has any evidence for the appearance of this new amino sugar-uridine complex in mammalian tissue.

DR. DORFMAN: We have no evidence, and it has so far not been found in mammalian tissue, to my knowledge.

REFERENCES

Glaser, L., and Brown, D. H. (1955). *Proc. nat. Acad. Sci.*, **41**, 253.
Park, J. T. (1952). *J. biol. Chem.*, **194**, 885.

Characterization of the Proteins from Human Synovial Fluid. By KARL SCHMID and MARGARET B. MACNAIR, *Boston, Mass.*

The proteins of synovial fluid have long been suspected of being identical with those of blood plasma. However, except for the identification of a few protein components by enzymatic or immunochemical methods, no systematic study has yet been carried out to establish the validity of this hypothesis.

The proteins of joint fluid, obtained from patients with rheumatoid and traumatic arthritis and neuro-arthropathy, and of plasma from the same individuals, were fractionated simultaneously by two methods. On the one hand, the proteins were separated by electrophoresis and identified by immunochemical reactions (Graber, 1955); on the other, they were fractionated according to their solubility (Cohn and others, 1946, 1950) and characterized by the following properties:

Distribution of the proteins among the fractions,
Content of protein-bound carbohydrate and cholesterol,
Electrophoretic mobilities and distribution.
Ultracentrifugal distribution and sedimentation constants.
Specific reactions such as clotting, ion-binding capacity (albumin, β1-metal-combining protein), reaction with cyanide ions (caeruloplasmin), titration of the iso-agglutinin, diphtheria antitoxin and antistreptolysin-O content, electrophoresis at *p*H 4·5, and immunochemical reactions by the Ouchterlony technique, using horse serum against human serum.

The results indicated that the proteins of pathological joint fluids are, for the most part, identical with those of plasma. In contrast to these similarities, differences were also noted. Besides variations in the total protein concentration (reported by others), a significant difference was observed in the relative amounts and distribution of the lipoproteins.

Discussion.—DR. WARD PIGMAN (*Birmingham, Ala.*): I should like to compliment Dr. Schmid on doing a very necessary piece of work. In the past it has simply been assumed that the synovial fluid components are very similar to those of other tissues. He has now demonstrated that the major components of arthritic fluids resemble those of blood very closely, as was earlier suspected. However, a considerable body of evidence indicates that, in the arthritic state, blood proteins are able to pass the synovial membrane and mix with the fluid more readily than usual. The real problem is the composition of the normal fluid. I know Dr. Schmid does not have the answer to this, but I think it is worth remembering that this work applies to arthritic fluids, where there is altered permeability and one would expect many blood components to enter the synovial space. What we do not know is what materials are present in normal synovial fluid. I hope that Dr. Schmid is able to continue this fine and tedious work until the full picture is completed.

DR. SCHMID: We are now in the process of studying *post-mortem* as well as normal synovial fluids. As far as we could determine by electrophoresis at *p*H 8·6 and 4·5, using hyaluronidase-treated fluid, we got the idea that their proteins do not differ significantly from those of pathological fluids except for the concentration.

In addition, I should like to mention that protein components which exist solely in synovial fluid are not excluded by the investigations I have just reported. For instance, one could imagine that the white cells could possibly release certain forms of nucleic acid. Perhaps one should also consider precursors of hyaluronic acid and collagen. Furthermore, we have noticed a component in Fraction V derived from pathological synovial fluids which is characterized by its yellow colour.

REFERENCES

Cohn, E. J., Gurd, F. R. N., and 12 others (1950). *J. Amer. chem. Soc.*, 72, 465.
——, Strong, L. E., and 5 others (1946). *Ibid.*, 68, 459.

Experimental Production of Arthritis in Rats. By CARL M. PEARSON, *Los Angeles, Calif.* (Introduced by Dr. Howard J. Weinberger.)

Freund-type water-in-oil adjuvant preparations containing heat-killed mycobacteria were combined with skeletal muscle from rats of the same strain used in the subsequent experiment, and these emulsions were given intracutaneously in the posterior cervical region to rats of the Wistar and Long-Evans strains. After a latent period of 2 to 6 weeks, varying degrees of acute inflammatory swelling developed in the ankles, the small joints of one or several paws, and the joints of the tail. After several weeks, periosteal reactions and exostoses were noted by *x*-ray in these regions. Histologically the reaction was one of intense granulation tissue proliferation with invasion of bone marrow spaces and the subchondral regions of the articular cartilages. In addition there were acute and chronic cellular infiltrations, hypertrophy of the synovia surrounding the joints and tendons productive of some tendonous adhesions, marked osteoblastic activity with periosteal osteogenesis, and some pannus formation in selected joints. Ankyloses, especially at the ankle and in the tail, were observed in some of the more chronic cases. Histologically these were formed by compact intra- and periarticular fibrous tissue. All other tissues were histologically negative, except for a granulomatous pneumonitis and an occasional small granuloma in the liver. Further experiments tended to show that the muscle may not be an essential constituent of the emulsion. Recently it has been noted that one subcutaneous injection into the dorsum of a single paw will produce reactions in another or all the remaining paws and in the tail in from 14 to 20 days.

Recently pleuropneumonia-like organisms of differing growth characteristics have been isolated from one of several joints in two of three animals so studied.

Discussion.—DR. MARIAN W. ROPES (*Boston, Mass.*): I think this is a fascinating paper, particularly since I have been interested in the pleuro-pneumonia-like organisms in relation to joint disease. I should be particularly interested in the effect on the organism of antibiotics, especially terramycin. It is difficult to interpret a histological reaction in relation to the role of the organisms, since we know far too little about the histology and course of pleuropneumonia arthritis in most animals.

DR. PEARSON: I am pleased you asked that question, Dr. Ropes, as it gives me a chance to expand. I have used antibiotics, streptomycin, terramycin, and penicillin, and I have noted, in general, that when I give the adjuvant injection into the paw, there has been an intense reaction at the local site rather than a subsidence of the reaction. The reaction did not subside after a few days, or continue to be repressed, but the ultimate result of alteration in the peripheral joints was largely suppressed. A small degree of peripheral reaction occurred in a significant number of animals. For instance, a series of fifteen that received terramycin had intense local reaction in the paw, and five of these developed mild degrees of peripheral reddening of the joints. However, this peripheral reaction was only detected on day-to-day observation of the animals, and if they had not been examined for two or three days, this information would probably not have been available.

DR. WALTER BAUER (*Boston, Mass.*): These observations are of interest and are reminiscent of previous reports on experimental arthritis. It has been known for some time that *Streptobacillus moniliformis* is a common inhabitant of the lung of rats. The lesions produced by these organisms are readily demonstrated at autopsy. The small cavities are filled with dry, insufflated, yellowish material.

Dr. Hans Selye has reported the production of arthritis in rats by placing unilaterally nephrectomized animals on a high salt diet. He has also reported on modifications

of this manner of inducing arthritis in rats. In addition, he has described what one might term "formalin arthritis". Dr. Pearson now reports on a form of arthritis occurring in rats receiving injections.

Did the rats used by Dr. Pearson harbour either *Streptobacillus moniliformis* or pleuropnemonia organisms? If so, do we have to entertain the possibility that the injections represented an insult, or if you prefer stress and strain, of sufficient magnitude to permit the previously harboured organisms to become pathogenic and thereby cause the arthritis?

Pathology of the type demonstrated by Dr. Pearson can, of course, be produced by any number of agents; chemicals, toxins, and bacteria (particularly streptococci of low-grade valence). In some instances, the arthritis, though acute in nature, may be short-lived. In some instances, it may last no more than days or weeks. If the arthritis induced is more chronic in nature, it is more likely to resemble the histological features considered consistent with those of rheumatoid arthritis.

These and other factors must be taken into account if we are to evaluate correctly the experimental arthritis report by Dr. Pearson.

DR. PEARSON: I should like to add that, in complete autopsy surveys of these animals, they have not shown any other consistent systemic lesion. The lungs have been clear except for what I call a granulomatous pneumonitis. This is not an infrequent finding following the injection of adjuvants and may be a reaction to some of the oil. Also, an occasional, small fibrotic granuloma has been noted in the liver.

DR. BAUER: Have you ever injected a normal rat joint with synovial fluid aspirated from an acutely involved joint?

DR. PEARSON: I have not.

DR. BAUER: If a living agent is responsible for the experimental arthritis, this is an extremely important and relatively simple experiment which should be done.

DR. PEARSON: I have taken some of the viable pleuropneumonia organisms that Dr. Dienes has forwarded to me, cultured them on pleuropneumonia media, and injected the viable organisms into the paws and intraperitoneally in rats. I have been able to obtain pure cultures from the paws. The animals have not developed any subsequent peri-arthritis.

However, in one series, I injected pleuropneumonia into the right paw and the adjuvant into the left paw. The pleuropneumonia reaction in the right paw subsided so that one could not tell that any injection had been given but in approximately two and a half weeks this area flared up again. This was probably a re-flare-up of the organism's activity, possibly under the stimulus of the action of the adjuvant which was present in the left paw.

DR. JOHN C. NUNEMAKER (*Arlington, Va.*): Many years ago, when Dr. Brown and I did our work on rat bite fever, most of our rats were of the Wistar strain. Later I spent 6 years in Salt Lake City where all of the rats were of the Sprague-Dawley strain. In those 6 years I was never able to get the *Streptobacillus* out of that strain, and I would, therefore, suggest you extend your observations to the Sprague-Dawley strain.

DR. PEARSON: Stoerk, Bielinski, and Budzilovich (1954) developed an arthritis which sounds very similar to mine. They injected Freund's adjuvant plus splenic extracts, and reported that antibiotics in large doses had no effect on this arthritis. They found no pleuro-pneumonia organisms.

DR. HOWARD J. WEINBERGER (*Beverley Hills, Calif.*): If it is true that the pleuropneumonia-like organism represents an unusual growth form of hormone commonly occurring in bacteria, then almost any Gram-negative bacillus that may be indigenous in some organ in the animal may give rise to one of the pleuropneumonia-like organism strains, which could be arthrotrophic and produce arthritis.

I should like to ask if Dr. Dienes did not attempt to reproduce the arthritis with the strain he recovered. The recovery of these organisms from the affected joints by Dr. Dienes and the attenuation or obliteration of the reaction with the antibiotics are strong evidences that the pleuropneumonia-like organism is responsible for the arthritis.

DR. PEARSON: I did not mention that because I am not certain of all the features. In the letter I received from Dr. Dienes he reported that he took some of these organisms and injected them into young rats and in 5 or 8 days the animals died. They had arthritis. He did not tell me the route of injection nor the dosage, so I have not repeated the experiment. I am not certain exactly what he did, but he mentioned that organisms were isolated from a joint and from the area of the tail.

DR. JOSEPH E. WARREN (*Pittsburgh, Pa*): Some of these lesions resemble those seen in the rat treated with growth hormone. Since it is known that cessation of ovarian activity in the rat has a tendency to increase the growth hormone, I wonder if the author has any evidence as to what happened to the oestrous cycles in these animals.

DR. PEARSON: I am sorry that I do not know what happened to the oestrous cycle. I might say we originally considered growth hormone as a possible factor. The reports on growth hormone do not suggest that these lesions are very similar to those produced thereby. There is certainly an over-proliferation of bone in both of these diseases, but the inflammatory reaction does not seem to occur in animals injected with the growth hormone.

DR. JEROME ROTSTEIN (*Minneapolis, Minn.*): In view of Lawrence's recent article, have you done any cell transfer studies?

DR. PEARSON: I have not done any chemical studies on the cell. I should first like to clarify in my own mind the role of these pleuro-pneumonia-like organisms before progressing further.

REFERENCES

Stoerk, H. C., Bielinski, T. C., and Budzilovich, T. (1954). *Amer. J. Path.*, **30**, 616.

Vascular and Articular Lesions of Frostbite. By J. P. KULKA and J. R. BLAIR, *Boston, Mass.*

The vascular and articular lesions occurring in frostbite are typically focal and resemble those of acute rheumatic diseases; a common pathogenic factor may be impairment of local blood flow. In frostbite the problem of the pathogenesis of these lesions is particularly well suited to experimental investigation: the intensity of

injury may be controlled; the initiating physico-chemical changes are relatively mild; and most of the tissue damage appears to develop as the result of endogenous processes after the aetiological exposure to cold is terminated.

Frostbite was produced in the feet of more than fifty rabbits by exposing them to air at −25° C. Discrete vascular and articular lesions developed within 24 hrs of exposure and resembled those of acute rheumatic disease in the following characteristic histological features:

(1) Localized necrosis.
(2) Rapid fragmentation of emigrated neutrophils.
(3) Deposition of amorphous fibrin-like material.
(4) Alteration of collagen bundles.
(5) Connective tissue hyperplasia.
(6) Slow repair resulting in dense scarring.

The vascular lesions were most prominent in arteries. They were typically segmental but increased in size and number after more severe degrees of exposure. The joint lesions were localized to the articular margins where the cartilage was in contact with vascular synovial tissue. Arthritis developed only when freezing had been relatively brief and the synovial circulation had been partially restored. Neutrophil infiltration began 3 to 9 hrs after exposure to cold and preceded the resorption of cartilage. At this time arteriospasm had been released, but most of the blood was flowing through arterio-venous channels and circulation through the minute vessels was intermittent and sluggish.

Two pathogenic processes are postulated to account for the development of the articular lesions:

(1) A primary cell injury representing an immediate effect of cold and resulting in leukotaxis.
(2) A histolytic process responsible for the resorption of cartilage and connective tissue matrix.

The latter process appears to be mediated by poorly diffusible or corpuscular elements of the blood such as the neutrophils which tend to accumulate in the initially injured tissues during the period of sluggish circulation. A similar haematogenous factor may be concerned in the segmental necrosis of blood vessels.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va*): Did Dr. Kulka study the effect of heparin on the development of the histological picture in these lesions?

DR. KULKA: No, we did not study the effect of heparin. It is one of the things we hope to do in the future.

Pathogenetic Significance of Fibrinoid and Plasma Cells in the Diffuse Collagen Diseases. By ROBERT H. MORE and HENRY Z. MOVAT, *Kingston, Ontario, Canada.*

Fibrinoid is a common feature in the lesions of the collagen diseases but haematoxylinophilia has been described as occurring only in disseminated lupus erythematosus. In turn, various investigators have postulated the origin of fibrinoid from either fibrin, degenerated collagen, or precipitated ground substance.

Morphological and tinctorial properties of fibrinoid derived from the following sources were studied: the diffuse collagen diseases; human and experimental hypersensitivity; and fibrinoid produced experimentally by various other means (mechanical, chemical, and physical). In all these instances the sequence of events showed the presence of fine strands of fibrin which later conglomerated to form masses showing all the characteristics of fibrinoid. These masses in turn showed the specific tinctorial properties of fibrin.

We were able to demonstrate that haematoxylinophilia and Feulgen positivity were properties of fibrinoid not only in disseminated lupus erythematosus but at times also in at least two other conditions: rheumatoid arthritis and polyarteritis nodosa.

Histochemically tyrosine, tryptophane, cystine, and cysteine were present in all the examples of fibrinoid studied. These amino acids were present in serum proteins but were absent or only present in low concentrations in collagen. Incubation of tissue with hyaluronidase altered the specific acid mucopolysaccharide staining material but not the fibrinoid. Trypsin resulted in the digestion of fibrinoid but not of collagen. Fibrinolysin led to the digestion of fibrinoid in frozen substituted tissue. These findings provide evidence for the almost certain origin of fibrinoid from fibrin.

Many of the mononuclear cells in the lesions studied were plasma cells in various phases of maturation. In serial time-studies of lesions of experimental hypersensitivity, plasma cells appeared in widespread fashion including the lesions typical of the collagen diseases.

Plasma cells are known to produce antibody. Their close association with the connective tissue lesions under consideration suggests that the latter are based on some aspect of local immune reaction. That they are not a response to connective tissue injury in evident because of their absence in association with fibrinoid produced by mechanical chemical or physical means. They are also absent in the passively-induced lesions of hypersensitivity.

These observations indicate the non-specific nature of fibrinoid as regards specific aetiology, but do point out the possible pathogenetic significance of the plasma cells as evidence of the hypersensitive nature of the "diffuse collagen diseases".

Discussion.—DR. D. MURRAY ANGEVINE (*Madison, Wis.*): About 10 years ago we gave a report on the nature of fibrinoid before this society, and it varied considerably from what Dr. More has said this morning.

I should first like to congratulate him on his presentation and on the excellence and quality of the staining. I should also like to point out that in 10 years histochemistry made a good many advances.

There are two differences in our studies. I believe the fibrinoid we described was rather more mature; it had been present for a longer time and was better developed. As he showed to-day, in the development of early acute lesions, it looks like fibrin and is fibrin. This shows the importance of studying the earliest lesions from the pathogenetic standpoint.

I should like to ask one question. In the late, well-formed fibrinoid nodules, for example, in the vegetations in the heart valves of rheumatic fever, such lesions do not stain with fibrin stains. I wonder if he can explain where the transition stage takes place?

DR. MORE: I think, in answer to the question posed by Dr. Angevine, I should start off from the first statement I made; that fibrinoid is an intensely eosinophilic or acidophilic material which is homogeneous and amorphous and possesses some of the tinctorial properties of fibrin. This is the only firm definition. It is not an exact physical chemical definition, but until the chemist has taken whatever we call fibrinoid and identified it as heterogeneous or homogeneous material chemically, we have no better way to define it.

In regard to the tinctorial properties of the material in the centre of old rheumatoid nodules, I would ask whether the material that Dr. Angevine has referred to is merely homogeneous and eosinophilic, or whether it is homogeneous and intensely eosinophilic? If it is the latter I believe it will possess the tinctorial properties of fibrin.

Some of the lesions we produced experimentally, first seemed to be homogeneous, but on careful study the borders were seen to be intensely eosinophilic, whereas the central parts were not so eosinophilic. The central parts do not stain with fibrin stains, whereas the peripheral portions do so.

It is our impression that this homogeneous, pink material is derived from blood plasma constituents, including fibrin, and that it is the fibrin component of the material that goes on to produce fibrinoid, whereas the other material may appear homogeneous and eosinophilic but without possessing all the tinctorial properties of fibrin proper.

DR. JEROME GROSS (*Boston, Mass.*): It may very well prove true that fibrin is an important component of fibrinoid, but with regard to the histochemical demonstrations, I think the conclusiveness of identification, in spite of the advances that Dr. Angevine has mentioned, is still not clearly established. Nor are these staining reactions numerous enough to allow reliable comparison.

It is interesting that you should say that the background of connective tissue and the cells give no positive Millon reaction for tyrosine, or Barnett reaction for sulphur-containing amino acid. The connective tissue has plenty of blood protein, and the cells are not collagenous and have plenty of tyrosine and sulphur-containing amino acids, which should also take the stain.

There may be a quantitative difference, but this does not consist in a difference in the type of protein present. For example, the compactness of material you show might be the cause of the intense staining. It could be the same stuff as is present in ground substance, but might differ in staining because of a greater density of substance. Perhaps, even in the cutting, you have a larger thickness of material which might be the same as in the normal connective tissue, but with different physical properties. All these things can give rise to difference in staining.

From my own experience, I know of some forms of collagen which, when stained with Mallory's connective tissue stain, will stain red while other forms will stain blue, yet they are all collagen.

DR. MORE: I think the questions raised by Dr. Gross are ones we are aware of. The failure to demonstrate material with the tinctorial properties of fibrin in normal connective tissue does not rule it out. The condensation of such hypothetical substance into visibly demonstrable fibrinoid during pathological alteration must be considered. However, in view of the presence of increased amounts of the normal constituents of connective tissue without the presence of fibrinoid on the one hand, and the presence of fibrinoid unassociated with increased amounts of the normal components of connective tissue on the other, it is doubtful whether condensation of the materials normally present in connective tissue would lead to the formation of fibrinoid. We are inclined to believe that there may be in pathological states an increase or swelling of the connective tissue components, as one manifestation of injury or repair, and in addition there may be exudation of foreign material which takes on the properties of fibrinoid.

DR. MORE: I am sure that when this work is published statements regarding fibrinoid will be phrased in such words.

DR. J. P. KULKA (*Boston, Mass.*): We have been interested in the same problem for some years and have arrived at almost identical conclusions.

The fibrin-like material in rheumatic lesions resembles the exudate of fibrinous pericarditis and the mural thrombi lining arterial aneurysms. It differs, however, from the delicate reticular form of fibrin which is characteristic of lobar pneumonia and other acute pyogenic processes; it is more compact, more resistant to resolution, and more likely to undergo slow organization. These properties of the fibrin-like material in lesions of rheumatic diseases are of interest because they may well be a factor in the tendency of such lesions to cause adhesion-formation, to heal slowly, and to result in dense hyalin scars.

DR. MORE: There is no doubt that a physiochemical change is produced. It does not have all the properties of fibrin, but it has some of them and that is why it has been likened to fibrin. What this physiochemical change means I do not know, except in regard to the one question that Dr. Kulka raises: it does not follow the same course as fibrin in terms of organization.

DR. WALTER BAUER (*Boston, Mass.*): Would it be more correct to conclude that there is a distinct possibility that fibrinoid arises from fibrin?

Purification of the Accessory Agglutinating Factor of the Serum in Rheumatoid Arthritis. By JOSEPH LOSPALLUTO and MORRIS ZIFF, *New York, N.Y.*

With the objective of isolating the sheep cell agglutinating factor, serum from patients with rheumatoid arthritis was fractionated by a number of methods.

On precipitation with ammonium sulphate, the agglutinating factor was obtained at concentrations of salt between 1·2 and 1·4 molar. This fraction yielded an active euglobulin when dialysed at *p*H 7. Treatment of this euglobulin by cold globulin precipitation yielded a fraction which contained all of the agglutinating activity of the original serum in 1·6 per cent. of the original nitrogen, a purification of about 60-fold. Electrophoresis of this product indicated the presence of at least two components with mobilities in the gamma- and beta- globulin range. The presence of inhibitor of sensitized sheep cell agglutination was demonstrable in rheumatoid as well as non-rheumatoid sera in globulin fractions precipitating at concentrations of ammonium sulphate higher than 1·4 M.

More complete purification of the agglutinating factor was achieved through the use of ion exchange chromatography. It was possible to obtain fractions purified

more than 500-fold over the original serum. Electrophoresis of a fraction prepared in this way showed the presence of two components with mobilities in the gamma-globulin range.

A number of properties of the agglutinating factor were studied. In experiments performed on the euglobulin fraction obtained by dialysis of rheumatoid serum at *p*H 7, complete loss of activity occurred at 100° C. after 30 min.; part of the activity remained after 30 min. at 78° C. The factor appeared to be stable over the *p*H range 4 to 11. Above and below these limits there was complete loss of activity. Enzymatic treatment of the euglobulin with trypsin or papain appeared to have no effect on its activity; little evidence of proteolysis was demonstrable.

Though the agglutinating factor occurs almost specifically in the serum of patients with rheumatoid arthritis, the inhibitor appears to be present in all human sera. In contrast to the agglutinating factor, inhibitor activity could not be concentrated in any single globulin fraction, but was precipitated over a wide range of salt and hydrogen ion concentration. It did not appear from the chromatographic data that the inhibitor was present in sufficient amounts to modify the agglutination titre of rheumatoid sera.

A Precipitin Reaction between Human Gamma Globulin and the Serum of Patients with Rheumatoid Arthritis. By WALLACE EPSTEIN, ALAN M. JOHNSON, and CHARLES RAGAN, *New York, N.Y.*

It has been established that the various serological tests used for the diagnosis of rheumatoid arthritis have a certain degree of specificity, and extensive investigations have been conducted in an effort to purify and characterize the "rheumatoid factor" present in a positive serum. These efforts have been hampered by the need for a sheep cell indicator system to detect its presence.

One of the sheep cell agglutination tests used is the gamma globulin (Fraction II) test which involves coating tannic-acid-treated sheep red cells with pooled human gamma globulin and suspending these cells in various dilutions of the patient's serum.

Current studies have revealed precipitate formation when pooled human gamma globulin is combined with the serum of patients having rheumatoid arthritis and a positive Fraction II test in the absence of sheep cells.

Dilution studies revealed characteristics of an antigen-antibody system between some constituents of pooled human gamma globulin functioning as an antigen and the rheumatoid factor as an antibody. By the quantitative precipitin technique, the relative weights of gamma globulin antigen and precipitate formation suggested that the antigen constitutes only a small fragment of the total gamma globulin. Precipitin curves suggested at least one interacting system using commercial liquid gamma globulin and at least two such precipitin systems using commercial powdered Fraction II.

In serums of patients having Fraction II titres of 7,000 to $>56{,}000$, 89 per cent. produced precipitates when commercial liquid gamma globulin was used, 100 per cent. when powdered Fraction II was used 61 per cent. revealed spontaneous precipitates in the cold which did not redissolve on heating.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va*): Dr. Epstein and his fellow-workers have certainly presented us with a very exciting new finding.

A year ago I had the pleasure of reporting to this group that the sensitized sheep cell factor can be absorbed by antigen-antibody precipitates prepared from rabbit immune sera. This was shown both by a reduction or disappearance of sensitized sheep cell activity after absorption of the serum by the precipitates and by the addition of protein nitrogen to the precipitates. When we first heard of Dr. Epstein's new finding, we were naturally interested to know how the material precipitable with Fraction II might be related to the material absorbable by rabbit immune precipitates. Correspondingly, four rheumatoid sera of various titres of sensitized sheep cell agglutinating activity were absorbed with egg-albumen anti-egg albumen rabbit immune precipitates. We then compared the amount of nitrogen precipitable by given quantities of Fraction II from aliquots of the absorbed and unabsorbed specimens. A marked reduction in the amount of precipitate was noted in the absorbed serum, indicating a definite relationship between the materials measured by these two techniques. It was significant to note, however, that the absorption with rabbit immune precipitate did not remove all material precipitable by Cohn Fraction II. These results are consistent with the presumption that the rheumatoid factor is auto-antibody having primary specificity to a normal component of human serum and cross-reacting with a component in rabbit serum.

It was of further interest to us to note that the amount of precipitate obtainable on addition of Fraction II to a rheumatoid serum is dependent upon the amount of dilution of the rheumatoid serum effected. Thus, when a quantity of Fraction II is added to a given rheumatoid serum in such concentration as to effect only a 4 : 5 dilution of the rheumatoid serum, little or no precipitate may be seen. However, when the same amount of Fraction II is added to the same amount of rheumatoid serum in a volume such as to provide a 1 : 5, 1 : 10, 1 : 20, or 1 : 40 dilution of the rheumatoid serum, an increasing amount of precipitate is formed, the curve plateauing at about 1 : 20. On analysing the supernatants, it was noted that one could detect neutralization of the rheumatoid factor without having the precipitates fully formed. Such discrepancy thus seen between agglutination end points and points of maximum precipitation may be of importance in interpreting the studies Dr. Epstein has just described to us. They indicate that caution must be taken in deciding whether or not we are dealing with two completely independent systems, as has been suggested, or whether we are dealing with a single system.

DR. EDWARD E. FISCHEL (*New York, N.Y.*): Does the rheumatoid serum spontaneously precipitate in the cold? What was the level of nitrogen in the blanks during the quantitative precipitin reactions. Was there a large amount of nitrogen or was it the usual trace amount?

DR. EPSTEIN: The serums used for quantitative precipitin studies were first centrifuged under refrigeration until no further spontaneous precipitate formation could be detected.

Quantitative measurements of the amount of spontaneous precipitate formed showed wide variations from

day to day in the same individual. Blood was allowed to clot at 37° C. for these studies.

Latex-Fixation Test in Rheumatoid Arthritis. By CHARLES M. PLOTZ and JACQUES SINGER, *New York, N.Y.*

One difficulty with the previously described serological tests for rheumatoid arthritis has been the introduction of extraneous biological properties related to the particles to be agglutinated (sheep erythrocytes, streptococci, etc.).

Polystyreme latex particles have been found by us to be suited to serological technique. In simple test these commercially obtainable particles were mixed with commercial gamma globulin and added to progressive dilutions of sera from patients with rheumatoid arthritis and a typical agglutination reaction occurred. The test can be done easily and in quantity in a single morning.

1,200 patients were tested by this carrier mechanism to which we have applied the name latex-fixation. 100 patients with the submitted clinical diagnosis of rheumatoid arthritis were tested by the latex-fixation method, the Rose-Ragan method, and the Fraction II technique of Heller. Positive percentage was almost identical: 12 patients negative to the Rose-Ragan test were positive by latex-fixation and four patients with 1:64 Rose-Ragan titres were negative to latex-fixation. With the latex-fixation test the doubtful group was eliminated, since either a strong positive or a negative was obtained. The overall incidence of false positive latex-fixation tests was less than 2 per cent., comparable to the other methods.

Various properties of latex particles, such as behaviour with various electrolytes and varying *p*H, and the use of the latex-fixation technique in other serological systems have been studied. The effect of the size of the particles, concentration of particles and antigen, temperature, shaking, centrifugation, and *p*H were studied.

The results indicate a rapid, technically easy, and reliable new test for rheumatoid arthritis. The carrier technique of latex-fixation has the experimental advantage of limiting the biologically active factors to gamma globulin and the serum being tested. The findings suggest the possibility that the nature of the agglutinating factor in the serum of patients with rheumatoid arthritis may be an auto-antibody against a gamma globulin.

Discussion.—DR. MORRIS ZIFF (*New York, N.Y.*): This is an intelligent approach to a method which gets us away from the infernal red cell and the necessity for inactivation of complement, and which avoids the tedious absorption of sera.

I suspect, from a practical point of view, that, in the long run, for diagnostic purposes we shall probably have to rely on some sort of agglutination test rather than on a precipitin test, since agglutination tests are, in general, more sensitive than precipitin tests.

I have analysed the relationships involved in the various tests described here at this meeting and at last year's meeting.

In the usual test, the red blood cell is sensitized with rabbit antibody or gamma globulin in the form of amboceptor. The sensitized cell, then, has the opportunity to react with the rheumatoid factor, presumably by virtue of combination between the rheumatoid factor and the rabbit antibody coating the red cell. When inhibition is carried out by addition to such a system of human euglobulin, the rheumatoid factor has two possibilities for reaction: it can attach itself to the red cell and if this occurs, agglutination take places. In the presence of excess of human gamma globulin, however, the reaction is probably forced by mass action towards a combination between the gamma globulin and the rheumatoid factor. The latter is then not left to react with the sensitized sheep cell and agglutination is inhibited.

The properties of tannic-acid-treated cells are apparently so altered that they can be more easily coated with proteins. In the Fraction II test, one has a sheep red cell which is coated with human gamma globulin, just as in the old tests the sheep red cell was coated by rabbit gamma globulin. The same sort of reaction takes place, in that the rheumatoid factor reacts with the coated red cell and agglutination occurs, this time on the basis of reaction with a gamma globulin coating which happens to be human rather than rabbit.

In the test just described by Drs. Plotz and Singer, one deals with latex particles instead of with the tannic-acid treated cell. This latex particle can apparently be coated when exposed to human gamma globulin, and can then react, by virtue of this coating, with the rheumatoid factors. As a result, the latex particle agglutinates. It has been shown that this reaction between the rheumatoid factor and gamma globulin can be demonstrated in a particle-free system in which the rheumatoid factor precipitates with human gamma globulin.

In all cases it would seem as though the essential reaction involved is one in which the rheumatoid factor reacts with a constituent of the gamma globulin, whether human, rabbit, or otherwise.

DR. GRACE P. KERBY (*Durham, N.C.*): I believe this technique is going to be of particular use in investigating some of the problems related to rheumatoid agglutination tests.

Our only experience in trying to substitute inert particles for the sheep cell was the use of ionic exchange resin particles, but we did not pursue this to the successful conclusion that Dr. Plotz has presented.

Our major experience has been with the more usual sheep cell technique, and we have varied only in that we have substituted Neurath's method of rapid mineral acid precipitation of the globulin fraction for the overnight dialysis technique. We have found that the preliminary absorption of serum is not necessary usually, appropriate controls being included to detect the occasional exception. With this technique we have had about the same results as are reported from other laboratories, i.e. about 85 per cent. positive in clinically unequivocal rheumatoids, and about 83 per cent. negative in all other patients with or without joint diseases.

As regards the specificity of these two techniques, it would seem that the sheep cell technique gives a somewhat larger percentage of positives in the clinically unequivocal rheumatoid group.

I noticed Dr. Plotz had one positive out of twenty patients with lupus erythematosus. Our experience has been that about half of these patients are positive. From that point of view, it would seem his technique has proved more specific than the sheep cell technique. I wonder if some of the difference may be due to the difference between using euglobulin fraction and using whole serum. I should be interested to hear any data on the use of the euglobulin fraction in the latex system.

I should be interested to hear what portion of the commercial gamma globulin fraction is the most active in the latex test, this because of the recent reports of the role of the basic fractions of gamma globulin in the flocculation tests. From our own quite preliminary observation in this direction, I suggest that in the rheumatoid tests as in flocculation tests, the more basic fractions of gamma globulin may prove to be the more active.

DR. JOHN H. VAUGHAN (*Richmond, Va*): I think it is important to take issue with one point raised in this discussion, and that is whether or not we are dealling with cells coated *just* with gamma globulin. I think it should be noted that this is gamma globulin on the cells plus the impurities in the gamma globulin preparation used to coat the cell. If you go back to some tanned cell studies which have been done with a much more purified protein than gamma globulin (*i.e.* crystalline egg albumen), it has been demonstrated by Dr. Stavitsky at Western Reserve University that components of egg white other than egg albumen can be responsible for the agglutination reaction of cells coated with crystalline egg albumen. So, I think one should always say very clearly that these cells are coated with gamma globulin, *plus* the impurities that were in the gamma globulin preparation.

Secondly, in terms of sheep cells coated with rabbit antibodies, we must again visualize that other substances besides the antibody may be in the cell coating. Components of serum complement may be present, as well as other more stable serum components. It can be shown, for instance, that when an Rh-positive red cell is particularly highly sensitized with anti-Rh antibody, the coated cell will apparently non-specifically absorb serum proteins other than complement.

Thus irrespective of the mode of coating cells for demonstrating the rheumatoid factor, it is necessary to remember that we have not yet attained a system that can be shown to give a single, well-defined coating material.

DR. PLOTZ: Commercially prepared gamma globulin is certainly an impure substance. I should like to reiterate that we have a number of presumably pure fractions that we are now trying to work with.

Also, I should like to make another point that I did make briefly in the paper: that the particles in about 80 per cent. of positives may be precipitated in the absence of gamma globulin.

Metabolic Effects of Aspirin Therapy in Rheumatoid Arthritis. By DANIEL M. BACHMAN, EVAN CALKINS, and WALTER BAUER, *Boston, Mass.*

Acetylsalicylic acid (aspirin), when administered in proper therapeutic dosage, remains the most efficacious drug in the long-term treatment of patients with rheumatoid arthritis; however, little is known concerning its metabolic effects in this disease. The present study was undertaken in order to survey some metabolic responses of patients with rheumatoid arthritis to therapeutic doses of aspirin.

Five patients with active rheumatoid arthritis were studied during control period and during periods when they received aspirin in daily doses of 3·3 to 6 g. Joint swelling, pain, and stiffness diminished during aspirin therapy and returned when aspirin was discontinued. Metabolic balance studies were performed on all patients. Investigation of acid-base balance included concurrent measurements of ventilation, urinary excretion of acid and of serum *p*H, and total CO_2 content.

Moderate doses of aspirin did not produce changes in the metabolic balances of nitrogen, sodium, potassium, calcium, phosphorus, or magnesium. Higher doses, accompanied by mild symptoms of toxicity, resulted in increased urinary excretion of nitrogen and phosphorus and in less positive nitrogen balances. Therapeutic doses of aspirin resulted in the following average changes:

Increased basal minute volume of ventilation (3 l./min.).
Decreased alveolar CO_2 tension (10 mm. Hg).
Increased B.M.R. (30 per cent. above control).
Decreased serum CO_2 content (8 mEq./l.).
Increased serum chloride (8 mEq./l.).
Decreased, increased, or unchanged serum *p*H.
Urinary excretion of ammonium increased (20 mEq./24 hours).
Urinary titratable acid increased (15 mEq./24 hours).
Urinary excretion of 17-OH corticosteroids or 17-ketosteroids unchanged.

Discussion.—DR. CHARLES M. PLOTZ (*New York, N.Y.*): Did you use any salicylates other than aspirin in your study?

DR. BACHMAN: This study was primarily concerned with the action of aspirin, but we have also compared the action of acetylsalicylic acid and sodium salicylate in the same patient. This patient was receiving a therapeutic dose of aspirin for several days before the beginning of the study and had a plasma salicylate level of 20 mg. per cent. at the beginning of the study. The patient was studied for 7 days during which she received aspirin, 8 days during which she received no medication, and 6 days during which she received sodium salicylate in chemically equivalent dosage. The actions of aspirins and sodium salicylate were similar, in that both produced increases in the minute volume of ventilation, decreases in total plasma CO_2 content, and slight rises in serum *p*H. The striking difference between the two compounds as shown by this particular study was the fact that aspirin therapy was accompanied by an increase in the urinary excretion of acid, whereas sodium salicylate therapy was accompanied by an initial transient fall in urinary acid excretion followed by a return to the control level. The patient was receiving a constant diet throughout the course of the study.

DR. PEARSON: You have talked primarily about patients with rheumatoid disease. Do you expect that normal people would react in the same way to aspirin as to the other salicylates?

DR. BACHMAN: There are a few studies in the literature pertaining to the effects of salicylates in normal individuals. Dr. J. H. Means, Emeritus Professor of Medicine at the Massachusetts General Hospital, studied the effect of salicylates upon basal metabolic rates of normal individuals as early as 1916. One of the most recent studies of the respiratory effects of the salicylates in normal individuals appears in a paper by Tenney and Miller (1955). They found effects upon respiration and

oxygen consumption similar to those seen in our patients with rheumatoid arthritis.

DR. RICHARD H. FREYBERG (*New York, N.Y.*): It was interesting to hear these important data concerning the metabolic effects of acetylsalicylic acid.

Was there any significant difference between the various female patients? or were there any differences between the sexes?

DR. BACHMAN: There were four female patients and only one male, so perhaps we should not conclude too much about sex differences. The data presented to-day were typical of the results in all five patients. It happened that some of these changes were of smaller magnitude in the male patient. I think this may have been due to the fact that the male patient received a smaller dose of salicylate in proportion to his bodyweight than did the female patients.

DR. OTTO STEINBROCKER (*New York, N.Y.*): Did you observe any correlation of the symptom response with the physiological or chemical reactions that occurred?

DR. BACHMAN: These patients all seemed to fare better when they were taking aspirin, in terms of obtaining relief from joint pain and stiffness, and often, subsidence of joint swelling. When we discontinued the aspirin, there was a return not only of pain and stiffness but, in several cases, of joint swelling and heat. We are unable to say anything at present about a possible correlation between the clinical state of the patient and the observed physiological findings.

DR. ROLAND DAVISON (*San Francisco, Calif.*): What did the figures for 17-ketosteroids and corticocoids show?

DR. BACHMAN: We did not determine these in all patients. The data obtained thus far show no significant change in the urinary excretion of either 17-hydroxycorticosteroids or 17-ketosteroids.

DR. JOHN C. SEED (*Scarsdale, N.Y.*): I should like to comment on the two most important factors influencing minute volume: oxygen consumption and responsiveness of the respiratory centre to carbon dioxide.

Any increase or decrease in oxygen consumption will cause a corresponding increase or decrease in carbon dioxide production. With a change in carbon dioxide production minute volume must change accordingly if homeostasis is to be maintained. Minute volume times carbon dioxide concentration in the expired air equals carbon dioxide excretion, and excretion must equal production for homeostasis. Indeed, excretion must equal production at all times, except for short periods of change from one set of equilibrium conditions to another.

With regard to the response of the respiratory centre to carbon dioxide, any factor such as aspirin which causes an increased response will cause an increase in minute volume, at the expense of homeostasis. In Dr. Bachman's work it would seem that both factors are active.

I wonder whether Dr. Bachman had any further comment upon the interrelationship between oxygen consumption and response of the respiratory centre or whether he has any idea why aspirin increases the metabolic rate.

DR. BACHMAN: You have drawn attention to a problem which is very difficult to answer: whether the increase in minute volume which we observed when the patients were in the basal state was due to acid-base adjustment, to a primary stimulating effect of salicylate on the respiratory centre, or to an increase in basal metabolism. At present, we are unable to say how much each factor contributed to the observed increases in basal minute volume. Neither can we conclude whether the changes in B.M.R. were primary or secondary to the respiratory changes. Tenney and Miller (1955) reported increased oxygen consumption in dogs given salicylates, and in the eviscerated animal, and in the curarized animal ventilated in a whole-body respirator. These workers have postulated that one site of action of salicylate might be the skeletal muscle.

REFERENCE

Tenney, S. M., and Miller, R. M. (1955). *Amer. J. Med.*, 19, 498.

Differential Diagnosis of Ankylosing Spondylitis. By JAMES SHARP, *Manchester, England.*

In approximately one-fifth of the patients attending a special spondylitis clinic, the clinical picture differed in various ways from that of classical ankylosing spondylitis, although most of them had bilateral radiographic changes in the sacro-iliac joints.

Analysis of the results of deep *x*-ray therapy revealed that those with straightforward ankylosing spondylitis were mostly much improved after this, but that the majority of the "atypical" cases were unimproved. These results could not be ascribed to longer duration of symptoms or to a preponderance of unusually severe cases in the atypical group.

As the effect of *x* rays appeared to be a local effect on irradiated tissues, these findings suggested that patients with "atypical" spondylitis might be suffering from other diseases resembling ankylosing spondylitis clinically but unresponsive to *x* rays. Some patients had psoriasis and others had features suggesting rheumatoid arthritis, recurrent rheumatic fever, or Reiter's disease with spinal involvement.

A study of other patients with these conditions revealed features by which they can usually be distinguished from ankylosing spondylitis. On review, approximately half of the atypical cases from the spondylitis clinic appeared to fit into the above categories. In some of the remainder, the spinal changes appeared to be due to osteo-arthritis, two had radiographic changes of "senile ankylosing hyperostosis", and two others had a heredofamilial form of spondylitis associated with calcinosis of limb joints and blood vessels. In a few patients the diagnosis remained obscure.

* * * *

FOUR PAPERS PRESENTED IN CONJUNCTION WITH THE AMERICAN COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

(1) Production of Auto-immune Bodies to Heart Tissue in Rabbits inoculated with Streptococcal Cultures. Nature and Histological Localization of the Reactive Antigen. By MELVIN H. KAPLAN, *Boston, Mass.* (Introduced by Benedict F. Massell.)

The inoculation of Group-A streptococcal cultures intradermally in rabbits was found to elicit the appear-

ance in the serum of complement-fixing antibodies to normal rabbit-heart tissue suspensions. Antibody titres reached a peak within 2 weeks after the inoculation and rarely persisted longer than 3 to 4 weeks. Repeated monthly injections for 1 year with small doses of streptococcal cultures of the same type or of successively different types, by either the intradermal or intravenous route, resulted in each case with a rapid rise and fall of antibody after each injection, and only rarely in a sustained elevated level. Heat-killed cultures also evoked antibody responses, which frequently were more marked than those evoked by live cultures. Culture filtrates or beef-heart medium alone were usually ineffective, but small transient rises were produced in a few animals. When the experiments were carried out with streptococci grown in a medium derived from a digest of casein and soy bean (trypticase-soy broth), antibodies to heart tissue were not found.

These results suggested that the active antigen eliciting the production of antibodies reactive with rabbit heart is a haptene with organ specific properties present in the beef-heart medium and absorbed by bacterial cells during growth. This interpretation is also supported by the observation that immunization of rabbits with beef-heart tissue suspensions has also evoked such complement fixing antibodies to rabbit-heart tissue. Chemical studies have thus far identified the substance in rabbit-heart tissue and in beef-heart medium as alcohol and ether soluble, precipitable by barium salts and presumably associated with a proteolipid. Immuno-histochemical identification of the antigen in rabbit-heart sections by a modified fluorescent antibody technique has revealed it within the sarcoplasm of the myocardial cell adjacent to the cell membrane and between the myofibrils, showing a distribution similar in some respects to that of myocardial cell lipid as detected by Sudan black or phosphine 3 R stains.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): Did you use only haemolytic streptococci of Group A?

DR. KAPLAN: We carried out our experiments with Group A of the various groups. We also carried out some control experiments with *Streptococcus viridans*, with which no antibodies to the heart were found. We did not use any groups other than Group A.

DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): Have you had an opportunity of observing the β-haemolytic streptococcus isolated from glomerulonephritis patients, with similar studies on the kidney?

DR. KAPLAN: We have not really carried out any detailed studies of this kind. Of course, we have used Type-12 strains. They show complement-fixing bodies to the heart. I am afraid we have nothing to say about work with the kidney.

(2) New Test for Inflammation. By ALVIN F. COBURN, EUGENE L. HESS, PRISCILLA H. MURPHY, and R. C. BATES, *Chicago, Ill.*

This test is for sialic acid (SiA test). The normal range of values for 85 children and adults in good health is 0·227 to 0·303. The range of values for three diseases studied was:

Disease	No. of Cases	Range
Acute rheumatic fever	37	0·372 to 0·592
Tuberculosis (different stages) . .	11	0·292 to 0·665
Cancer (different stages) . .	6	0·332 to 0·590

The test involves the use of only three materials:

(1) 10 per cent. trichloracetic acid.
(2) Glacial acetic acid.
(3) Concentrated sulphuric acid.

In comparison with results obtained on diphenymanine determinations from 68 consecutive rheumatic patients we obtained the following:

(*a*) *Agreement.*—D.P.A. positive, sialic acid positive 178 out of 318.
(*b*) *Agreement.*—D.P.A. negative, sialic acid negative, 95 out of 318.
(*c*) *Disagreement.*—D.P.A. positive, sialic acid negative, 2 out of 318.
(*d*) *Disagreement.*—D.P.A. negative, sialic acid positive, 41 out of 318.

Serial determinations showed that the SiA test, compared with the erythrocyte sedimentation rate (Wintrobe) appeared to be a more sensitive expression of persistent rheumatic inflammation. The return to normal values in eighteen patients studied was slower in twelve and coincidental in five, but in one case the erythrocyte sedimentation rate followed the SiA. The average difference in return to normal values was 2 weeks slower for the SiA test.

The SiA test is easy to perform, gives reproducible results, and reflects minimal inflammation.

(3) Zone Electrophoresis in Studies of Polysaccharides in Sera from Patients with Rheumatic Fever and Rheumatoid Arthritis. By WILLIAM J. KUHNS and PATRICIA J. HYLAND, *Pittsburgh, Pa.*

Electrophoretic fractions of sera show quantitative changes in the course of acute rheumatic fever and active rheumatoid arthritis. Elevations of alpha- beta- and gamma-globulins are observed in both conditions; in rheumatoid disease the albumin fraction is frequently decreased. These changes revert toward normal spontaneous remissions or successful response to treatment. Serum polysaccharides, as determined by several methods, increase in the course of these illnesses and decrease as inflammatory activity subsides. The purpose of the present investigation was to study polysaccharides of serum fractions separated by the method of paper electrophoresis. In order better to characterize mucoproteins, electrophoresis of sera was carried out both at *p*H 4·5 and 8·6. Analyses were run in triplicate so that migrated fractions on each sheet of paper could be stained separately with the following reagents:

(*a*) bromphenol blue,
(*b*) basic fuchsin,
(*c*) toluidine blue.

Separate visualization of serum protein fractions was possible after the application of bromphenol blue. Polysaccharide components were visualized with basic fuchsin if they contained "1,2 glycol" groupings which were oxidizable to aldehydes, or with toluidine blue if they were capable of being stained metachromatically. When electrophoresis of sera was carried out at *p*H 8·6, protein-bound polysaccharides associated with the alpha-globulins were most generally increased in blood from persons with active disease, and they returned to normal as activity subsided. Mucoproteins separated electrophoretically at *p*H 4·5 also paralleled the degree of disease activity. This was observed in both M-1 and M-2 components. There were no significant differences between the stained patterns of sera from patients with acute rheumatic fever and those of sera from persons with active inflammatory rheumatoid arthritis. In patients with rheumatoid arthritis no consistent parallelism was found between sheep cell agglutination titres and amounts of polysaccharide, since sheep cell titres remained significantly high even after successful response to treatment and a return to normal of the electrophoretic components.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va*): Have you studied any other generalized diseases that do not involve the connective tissue which might have an increased sedimentation rate, such as hepatitis or generalized carcinoma, and would these also provide the elevated serum polysaccharides.

It might be worth pointing out that when one has a large amount of gamma-globulin in a serum, particular pains are necessary to determine whether a higher beta-globulin peak represents anything other than more gamma-globulin, inasmuch as it has been demonstrated from immuno-electrophoresis that gamma-globulin can have the mobility of beta-globulin.

DR. KUHNS: This test (periodic acid-Schiff stain) does not necessarily differentiate between various diseases on the basis of abnormalities in serum polysaccharides. In this sense, the test is non-specific, as are other tests for inflammatory activity. We have examined serum from patients with liver disease and with malignancy, and they have shown stained electrophoretic patterns which are very similar to those seen in inflammatory states such as rheumatoid arthritis.

DR. JEROME ROTSTEIN (*Minneapolis, Minn.*): Is there any chronological sequence in the amounts of polysaccharide that arise, as in Ropes' work where they showed the beta-globulin followed by gamma-globulin?

DR. KUHNS: Do you mean proteins or polysaccharides?

DR. ROTSTEIN: Is there any chronological relationship between the globulin and polysaccharide elevations?

DR. KUHNS: It has been asked whether abnormal changes in serum proteins and polysaccharides were parallel as indicated by the respective stains, or whether there was any evidence of divergence between the protein and polysaccharide content of a fraction with changes in disease. In our experience, the bromphenol blue and the periodic acid-Schiff stains reflected similar proportional changes in the same serum globulins during the course of rheumatoid arthritis.

DR. WILLIAM K. ISHMAEL (*Oklahoma City, Okla*): I think there is a definite relationship between inflammatory activity and elevation of the protein-bound polysaccharide. We found, in gravitating the inflammatory reaction, that it is better to express serum polysaccharide in relation to serum protein (polysaccharide-protein ratio). This gives you a more significant correlation coefficient with the inflammatory reaction.

DR. KUHNS: Is this the tryptophane?

DR. ISHMAEL: Yes, the Shetlar method.

DR. KUHNS: The matter of defining the method employed was taken into consideration, since there are several indices, those used for estimating the nucleoproteins such as tyrosine content or total protein content.

DR. ISHMAEL: We are preparing our material for publication on paper electrophoresis analysis of glycoprotein fractions. This data grossly correlates well with the chemical method and does indeed have considerable promise.

DR. KUHNS: I am sure, for instance, in comparing the starch method, to estimate tyrosine and tryptophane, there was a difference in the amount of material observed as compared with the amount of Schiff staining material in corresponding serum. So defining the method is important.

DR. EUGENE L. HESS (*Chicago, Ill.*): I am a member of the Rheumatic Fever Institute and a co-author of the preceding paper. I wish to correlate the two papers, in that the paper presented by Dr. Kuhns demonstrates, I think, very well, the rise in the poly-saccharide-containing components in serum. It is well established that in almost any type of inflammation this rise is a commonly observed phenomenon. This has been shown by moving boundary electrophoresis by chemical methods, and very well by Dr. Kuhns.

It has also been quite well established that sialic acid is a common constituent of the mucoproteins present in the alpha-globulin fraction of serum. The test described by Dr. Coburn in the preceding paper appears to be specific for sialic acid, and therefore for mucoproteins.

The method described by Coburn is a variation of an earlier colorimetric method employing diphenylamine reagent. Anderson and MacLagan (1955) in England have stated that the diphenylamine test appears to be specific for mucoproteins.

I think that it is interesting to note that the methods described in these two papers measure essentially the same thing, the rise in mucoprotein levels in serum during inflammation: one by a physical technique and the other by a chemical technique.

DR. MELVIN H. KAPLAN (*Boston, Mass.*): Did Dr. Kuhns carry out any lipid stains in association with the M-1 and M-2 spots?

DR. KUHNS: We have already carried out lipid stains and we have studied electrophoretic serum fractions from patients with rheumatoid arthritis using Sudan black stain, but there seems to be no correlation between the amount of stained material and clinical status. However, there is evidence that Sudan black does not give a true picture of the lipid material contained in serum (Davis, 1955). This subject requires further investigation.

DR. GRACE P. KERBY (*Durham, N.C.*): Dr. Kuhns mentioned using toluidine blue stain on the electrophoresis strips to demonstrate certain polysaccharides in serum, and one presumes that this was for checking on the presence of mucopolysaccharides. It seems quite clear now that mucopolysaccharide-like substances are

present in serum, apparently closely associated with certain globulin fractions, as reported by Badin, Schubert, and Vouras (1955), and by Schiller and Dewey (1956). Our own experience confirms this in the course of studying these materials in plasma. However, it has been our experience that the toluidine blue stain will not satisfactorily demonstrate the metachromasia of these substances while they are still associated with proteins. If separated and concentrated for electrophoresis in a form suitable for later toluidine blue staining, the factors used for electrophoresis in the present study would probably not have been suitable for these fast-moving components.

I wonder if Dr. Kuhns has any further studies on these polysaccharide fractions in the serum he has studied.

DR. KUHNS: We reported that electrophoretic patterns treated with toluidine blue gave uniformly negative results in regard to the ability of fractions to be stained metachromatically. Dr. Kerby has asked if our negative results with the toluidine blue stain might have been due to the inability of this stain to produce metachromasia in protein-bound polysaccharides as they occur in the major electrophoretic fractions. We have not as yet carried out further work with toluidine blue, but as she has suggested, split products (obtained, for example, by hydrolysis) processes from zone electrophoresis eluates might be worthy of additional studies in this respect.

REFERENCES

Anderson, A. J., and MacLagan, N. F. (1955). *Biochem. J.*, 59, 638.
Badin, J., Schubert, M., and Vouras, M. (1955). *J. clin. Invest.*, 34, 1317.
Davis, H. L. (1955). "Studies of Swahn Method for Blood Lipids." Amer. Chem. Soc., Minneapolis, September 11-16, 1955.
Schiller, S., and Dewey, K. F. (1956). *Fed. Proc.*, 15, 348.

(4) Mass Penicillin Prophylaxis in the Control of Civilian Streptococcal Epidemics. By DAVID C. POSKANZER, *Albany, N.Y.*, HARRY A. FELDMAN, and WILLIAM G. BEADENKOPF, *Syracuse, N.Y.*

The occurrence of acute streptococcal epidemics among students attending central schools in two upstate New York communities presented us with unusual opportunities to study their epidemiology and to evaluate two different methods for their control. Although a number of mass prophylaxis experiments have been reported from various military groups, comparable data is not available from civilian populations. The latter are of particular importance, not only because of the absenteeism which the streptococcal epidemic induces, but because it would be particularly advantageous to curb streptococcal infections among school children where the hazards of complications such as rheumatic fever are particularly great. In the one community, 95 per cent. of the school population of 500 students, school teachers, bus drivers, and administrative personnel received 250,000 units of penicillin G, twice daily for 10 consecutive days. Permission to provide such treatment was obtained from almost all parents, and the drugs were administered by the home room teachers. Each pupil was given a suitable number of pills to take home for the week-end. Children who had histories of penicillin sensitivity were given tetracycline, 250 mg. twice daily, in place of the penicillin. 24 per cent. of the students, administrative and teaching staffs, and bus drivers were cultured before the institution of therapy. Subsequent follow-up cultures were obtained on the seventh day of treatment, and on the 24th and 62nd days, and all streptococcal strains were grouped and typed. Of the initial cultures, 31 per cent. were of Group A, whereas 0 per cent. of the 7th day, 5 per cent. of the 24th day, and 10 per cent. of the 62nd day cultures were of this group. Streptococcal cases disappeared quickly, and this was reflected in a decrease in carriers. Absenteeism rapidly diminished to the expected normal rate for the season.

In the other community, essentially the same kind of procedure was followed, except that the penicillin treatment consisted of one tablet of 250,000 units penicillin G on each of 10 consecutive days. Of the culture sample obtained the day before treatment was begun, 38 per cent. contained Group A streptococci; this fell only to 20 per cent. on the 10th day (last day of treatment) and it rose to 32 per cent. on the 24th day, and 38 per cent. on the 55th day. The disease rate followed this curve, and shortly after the last culture sample was obtained the school authorities closed the school. Additionally, in this second community, the families of 56 students were cultured before the institution of treatment and several weeks after its completion. The non-school family members were not treated but were studied for the frequency of streptococci among them in relation to the school population.

Only one penicillin reaction was observed in both studies and that occurred in an adult. It is of interest that more successful regimen is similar to that which has been found most effective in military studies.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): It seems to me that one of the most important aspects of this paper is its bearing on current views on the prophylaxis of rheumatic fever by prevention of streptococcal infection.

I gather from your data that positive cultures were present before the penicillin was given in the majority of instances, and that when cultures were positive later it represented the reappearance of the same streptococcal strain that the patient had carried before treatment was begun.

I wonder how many of your patients with positive cultures after penicillin had been started, were patients whose throat culture had been negative at the start and became positive later.

May I have an answer to that question before I comment further?

DR. POSKANZER: Only one individual acquired streptococci during the course of the study. There were a large number who retained the same type during the 10 days of therapy.

DR. CURRIER MCEWEN (*New York, N.Y.*): Then, if I may comment further it seems to me that this is of key importance in the whole programme of penicillin prophylaxis or rheumatic fever prophylaxis as advised by the American Heart Association, on the recommendation of the Committee on Prophylaxis of the American Council on Rheumatic Fever and Congenital Heart Disease. In the regimens recommended there is a very sharp difference between that for continuous prophylaxis to prevent the occurrence of haemolytic streptococcal throat infections in patients who do not already have them, and

that for the patient who is already infected. The prevention can be achieved with relatively low blood levels, but, it takes a higher blood level to get rid of the carrier state in the patient who is already infected.

It is important for us to have that in mind in interpreting your results, because they bear out very emphatically the importance of the regimen recommended by the American Heart Association, namely, that if one is attempting to clear up a haemolytic streptococcal carrier state which is already present, a single dose of 250,000 units of oral penicillin a day for 10 days is not enough. Indeed, the recommendation of the American Heart Association for this purpose is 250,000 units three times a day, and the dose of 250,000 units once a day is recommended only for continuous prophylaxis to prevent fresh infections.

Dr. Poskanzer's report is a very clear demonstration of the fact that one must use more than one oral dose a day to wipe out infection which is already present, and, also, that it is necessary to continue that prophylaxis for the full 10-day period rather than just for a couple of days, as is so commonly done.

DR. ALVIN F. COBURN (*Chicago, Ill.*): I should like to emphasize one point which is frequently neglected, and that is that strains of the haemolytic streptococcus may vary greatly in their sensitivity to anti-bacterial agents.

It has been difficult and is perhaps still impossible to know what the future will bring forth in the sensitivity of Group A streptococci to antibiotics. When penicillin was first being tested it was given by us intramuscularly, 1,000,000 units a day for 4 days. One group of ten men, all of whom had Type 6 in their throat flora, developed negative throat cultures. A week later haemolytic streptococcus Type 6 reappeared in the throats of six or seven out of the ten patients, and one developed a bronchopneumonia.

More recently we had in our staff an outbreak of pharyngitis with Type 19. We were especially anxious to have these persons on duty, they were given 1,000,000 units of penicillin a day in five oral doses. At the end of 5 days penicillin was discontinued. Six out of nine of this group not only developed positive throat cultures but also evidences of disease with slight fever and sore throat. Each recurrence was accompanied by Type 19 in the throat flora. Five had repeated 5-day courses, but one of them remained a carrier for months.

It seems to me possible that, whereas 250,000 units or 500,000 units may be effective as prophylaxis for certain strains of haemolytic streptococcus, there will be others, either present now or to come in the future, that will require a yet larger dose of penicillin to give effective results.

DR. POSKANZER: As far as I am aware, there is no published evidence indicating that there is a difference in sensitivity to penicillin among the various types of Group A streptococci. We have evidence that there is a difference in sensitivity among the different groups, and that among these groups, non-Group A streptococci appear to be more resistant than the Group A organisms.

DR. MILTON MARKOWITZ (*Baltimore, Md.*): It is appropriate to mention a recent epidemic of streptococcal infection that occurred in a convalescent home for rheumatic patients, where we followed the recommendation of the American Heart Association, and used 200,000 units of oral penicillin once a day among children who received the drug under close observation. I might also add that our own previous experience with this dosage was good.

During the outbreak in question we found that eleven of the 33 patients developed clear evidence of Group A infections. I think one-third of these quite clearly indicates a failure of 200,000 units once a day to prevent streptococcal infections.

The material presented here points out that there may be a dosage factor for the prevention of streptococcal disease, particularly in a semi-closed community where there is repeated exposure to a virulent organism.

It would be advisable for the future recommendations of the Heart Association to take this into account.

DR. CURRIER MCEWEN (*New York, N.Y.*): Could I make just one further comment concerning our experience in Baltimore?

At a recent meeting of the Council on Rheumatic Fever and Congenital Heart Disease there was discussion of some data which suggest that, even for continuous prophylaxis, a single dose of 250,000 units daily may be insufficient. This, however, is not yet certain.

DR. POSKANZER: I was not aware this recommendation was forthcoming.

DR. G. H. STOLLERMAN (*Chicago, Ill.*): As a member of the rheumatic fever prevention committee of the Council on Rheumatic Fever and Congenital Heart Disease, I feel I should comment at this point.

The revised recommendations of the committee are not yet ready for official release. Inasmuch as Dr. McEwen has indicated that there will be a change in the recommended dose schedule of oral penicillin for continuous prophylaxis in the rheumatic subject, I think a word of explanation is in order. The committee will suggest that it is safer to administer 200,000 to 250,000 units of penicillin orally *twice daily*, rather than once daily.

This change is not based on any evidence that the resistance of Group A streptococci to penicillin has changed. Rather, it is based on reports from a few studies in progress which indicate a somewhat higher incidence of breaks-through of streptococcal infection than was anticipated in patients receiving single daily doses of 200,000 units of penicillin orally. When such breaks-through have occurred the organisms have not been penicillin resistant. It is difficult to interpret whether such breaks-through are based upon poor co-operation of the patient, that is, failure to take medication regularly, or whether the dose itself is inadequate.

In some studies, like those of Dr. Markowitz previously mentioned, some breaks-through have occurred in patients who apparently have taken medication faithfully; the committee therefore considered a dose given twice daily as a safer recommendation, so that there is less chance of a full day's prophylaxis being omitted. The recommendation does not mean there is any known change in the virulence or penicillin sensitivity of the streptococcus.

I should also like to comment on the implications of the present study with regard to the prevention of first attacks of rheumatic fever. Under present civilian conditions, the most common source of streptococcal epidemics is in school children, especially the younger age groups. With more careful studies of such epidemics and adequate public health measures designed for their early detection, we should be in a position to stamp them out promptly by the proper penicillin treatment of patients and contacts in the fashion presented by the authors. This should reduce the incidence of rheumatic fever significantly. Minor differences in the penicillin doses employed to treat streptococcal pharyngitis successfully

are difficult to interpret, but there is general agreement that, if oral penicillin is used, at least 500,000 units or more must be given daily for at least 10 days. If penicillin is used parenterally, a single dose of 600,000 to 1,200,000 units of benzathine penicillin should be adequate.

Dr. JOSEPH E. WARREN (*Pittsburgh, Pa*): I hope some of the people reporting such "breaks-through" in penicillin prophylaxis will take the opportunity later to retest the same patients to see if they effectively absorb penicillin.

DR. DAVID C. POSKANZER (*Albany, N.Y.*): One of the important points demonstrated by this study is that mass prophylaxis in school groups is a practical measure. We were impressed with the efficiency with which the school administration managed the programme. It appears that this method may have wide application in school epidemics.

* * * *

Corticosterone Secretion and Metabolism in Normal Children and in Patients with Rheumatic Diseases. By EDWIN R. HUGHES and ROBERT S. ELY, *Salt Lake City, Utah.* (Introduced by Dr. Vincent C. Kelley.)

The role of adrenocortical steroids in the production of collagen diseases clinically is largely speculative. However, the beneficial results of hormone therapy in such diseases, and the production of similar lesions experimentally indicate that this role is fundamental. Moreover, the evidence of a change occurring with age in the pattern of adrenocortical secretion might help further in explaining the differences observed between children and adults in the clinical manifestations of collagen diseases.

In these studies, plasma steroids were measured in children of different ages and in subjects with rheumatic disease. Plasma 17-hydroxycorticosteroids were determined by the method of Nelson and Samuels (1952) Corticosterone (Compound B) was measured by a modification of the fluorometric method of Sweat, a technique which also measures 17-hydroxycorticosterone (Compound F). In the fluorometric method, the elution fraction containing Compound B may also contain other substances with fluorescent activity, for simplicity, however, this elution fraction will be called "Compound B".

In normal age groups, the mean B values of $5 \cdot 5 \pm 0 \cdot 58$ μg. per cent. for cord blood and $4 \cdot 9 \pm 0 \cdot 65$ μg. per cent. for the first week of life were significantly greater than those of $3 \cdot 2 \pm 0 \cdot 45$ μg. per cent. for the 6 to 17-year age group and $3 \cdot 0 \pm 0 \cdot 21$ μg. per cent. for adults. The increase in Compound B levels in response to ACTH was 4 to 5 μg. per cent. (over fasting levels) in children under 10 years, but only $1 \cdot 5$ μg. per cent. in the 11 to 17-year age group.

In different collagen disease groups, the mean levels for Compound were elevated over normal: 5-6 μg. per cent., compared with $3 \cdot 2$ μg. per cent. Also, the B response to ACTH was much greater in collagen diseases: an increase of $6 \cdot 6 \pm 0 \cdot 55$ μg. per cent. compared with $2 \cdot 9 \pm 0 \cdot 61$ μg. per cent. Compound B values also were significantly elevated in inactive rheumatic children and their parents, but were only equivocally elevated in their siblings.

In normal subjects, 17-hydroxycorticosteroid and Compound F responses to ACTH were of similar magnitude. However, in subjects with collagen disease, the 17-hydroxycorticosteroid response was significantly greater than that for Compound F.

After the exogenous administration of Compound B, normal children had a B half-life of $39 \pm 2 \cdot 7$ min.; in contrast, children with active collagen disease had a B half-life of $69 \pm 6 \cdot 7$ min. Similar studies for Compound F showed a definite prolongation of the half-life in children with active collagen disease, but an essentially normal half-life with inactive disease.

Thus, it appears that Compound B values are influenced by a factor of age and that the secretion and metabolism of certain corticosteroids are altered in children with collagen diseases.

Discussion.—DR. JAMES B. WYNGAARDEN (*Bethesda, Md*): I should like to speak briefly about the measurement of corticosterone in human plasma, by an isotope dilution technique developed at the National Institutes of Health by my associate, Dr. Ralph E. Peterson. In this method, the steroids are extracted from plasma with methylene chloride. This extract then contains a number of steroids and other substances, including a minute quantity of corticosterone. To this extract is added a small quantity of corticosterone labelled in carbon-4 with C^{14}. The extract is then chromatographed on paper, and the corticosterone eluted from it. One fraction of the eluate is then analysed for C^{14} content, and another for corticosterone by a fluorescence technique. From these determinations the specific activity of the corticosterone may be calculated and compared with that of the labelled corticocosterone originally added. From the change in specific activity of the corticosterone a dilution factor may be calculated. This is a measure, in turn, of the amount of corticosterone originally present in the extract of plasma, and from knowledge of this value the concentration of corticosterone in 100 ml. plasma may readily be obtained. This is a sensitive, accurate, and specific method.

By this method the level of corticosterone in plasma is considerably lower than that reported here to-day, and also considerably lower than those obtained with other methods by other investigators. The true corticosterone level appears to be about 1μg. per cent. in normal adults, ranging from $0 \cdot 5$ to $2 \cdot 1$ μg.

I think the non-specificity of the technique employed in the present study limits somewhat the confidence one can place in corticosterone levels of 3μg. per cent. or more, and also that in the interpretation of the changes reported. It would be interesting to repeat these studies with the more specific method for corticosterone determination developed by Dr. Peterson.

DR. GERALD P. RODNAN (*Pittsburgh, Pa*): Study of children with other categories of illness, as well as of healthy children, would provide more adequate "control" data for interpretation of the findings just presented. I wonder whether the speaker has such information on other disease states apart from the collagen group.

DR. HUGHES: I appreciate the validity of the comments made by Dr. Wyngaarden. We realize that this tech-

nique does not measure corticosterone. We have done many studies with it, and in our perfusion work and in animals that have corticosterone in the principal circulating steroid, we have found it reproducible and quite valuable.

With regard Dr. Rodnan's question, we have no such data at present, but are in the process of collecting it.

DR. JOSEPH J. BUNIM (*Bethesda, Md*): I should like to add to Dr. Wyngaarden's comments on the results obtained in the laboratory with Dr. Peterson at Bethesda. In a group of about eight patients with active rheumatoid arthritis, all adults, there was no significant difference from normal in the plasma level of hydrocortisone, or in the half-time its rate of disappearance from the plasma, or in the total urinary excretion of 17-hydroxycorticosteroids or 17-ketosteroids in patients with active rheumatoid arthritis.

DR. HUGHES: I am not aware of that. I have no explanation for the difference.

REFERENCES

Nelson, D. H., and Samuels, L. T. (1952). *J. clin. Endocrinol.* 12, 519.

Peterson, R. E. (1956). *J. biol. Chem.* (In the press.)

Hydrocortisone in Plasma of Normal Individuals and Patients with Certain Rheumatic Diseases. By L. EMMERSON WARD, CHUNG WU, PHILIP S. HENCH, HAROLD L. MASON, CHARLES H. SLOCUMB, HOWARD F. POLLEY, and JOHN G. MAYNE, *Rochester, Minn.*

Recent developments in methods of measuring steroids in the blood have enabled studies to be undertaken of the metabolism of these substances in normal individuals and in patients with various diseases. Hydrocortisone is probably the main normal adrenocortical product of man, although by no means the only one. The Silber-Porter method offers a convenient measurement of hydrocortisone in plasma; normally free hydrocortisone probably accounts for about 95 per cent. of the yellow colour which develops in the Porter-Silber reaction when an appropriately treated extract of plasma reacts with phenylhydrazine in sulphuric acid. The same method also can be applied to the measurement of plasma concentrations of cortisone and various antirheumatic analogues of the 17-hydroxycorticosteroids.

Contrary to conjecture, the plasma content of hydrocortisone does not remain relatively constant for 24 hrs, nor does it fluctuate notably in response to the usual minor stresses which occur in the course of ordinary daily activities. Instead, plasma concentrations of hydrocortisone in normal individuals exhibit a characteristic diurnal rhythm, levels generally being higher in the early morning, decreasing as the day progresses, and rising again the next morning. This diurnal pattern is also seen in patients with various rheumatic diseases.

The plasma concentrations of hydrocortisone, or its analogues (as measured by a modification of the Silber-Porter method) in normal persons and in patients with certain rheumatic diseases have been measured at different times of the day and the influence of certain physical and therapeutic agents (including salicylates, cortisone, corticotropin, hydrocortisone, prednisone, and prednisolone) and certain stresses have been observed.

Diurnal Plasma Corticoid Studies and their relation to Morning Stiffness in Rheumatoid Arthritis. By JOSEPH E. WARREN, *Pittsburgh, Pa.*

Since the plasma concentration of free hydrocortisone probably reflects most closely the amounts available to the tissues, we have measured these plasma levels in a series of ten normal and fourteen rheumatoid subjects.

Studies by others have demonstrated in normal subjects that the lowest concentration occurs at night and that peak levels occur at 8 a.m. Thus the eosinopenia and uricosuria which reach their maxima at 11 a.m. in normals are metabolic effects of the preceding high hydrocortisone levels.

Patients with rheumatoid arthritis suffer from stiffness on arising in the morning. This symptom disappears in the next few hours. We thought this relief of stiffness might also represent an effect of the higher morning levels of hydrocortisone.

We therefore measured the plasma corticoids around the clock at 3½-hr intervals. The rheumatoid patients had mildly to moderately active disease. None had fever nor had they been on hormonal therapy. Aspirin was omitted on the preceding morning. The 7 a.m. specimen was drawn before the subjects were allowed out of bed, usually within a few minutes of awakening.

In normal subjects the low point was observed at midnight or 3.30 a.m., whereas the peak levels were at 7 or 10 a.m. This agrees with the observations of other workers.

In the rheumatoid patients a normal pattern was seen in two with minimal rheumatoid activity. In the others the concentrations at 3.30 a.m. were higher than normal and showed a smaller rise toward 7 a.m. Thus the peak concentration appears at 7 a.m. and could explain the disappearance of stiffness during the later part of the morning. We have no satisfactory explanation for the higher levels in the rheumatoid patients at 3.30 a.m.

Discussion.—DR. RICHARD D. MILLER (*Pasadena, Calif.*): In two patients with severe acute rheumatoid arthritis, we have done a complete adrenalectomy. We have observed these patients for almost 2 years since surgery. Stiffness has virtually disappeared in both of them, although there is some pain and some minor swelling.

PRESIDENT ROBINSON: Those patients obviously were maintained on corticosteroid therapy.

DR. MILLER: The two patients referred to were on steroid therapy for 4 years before surgery and both had severe rheumatoid arthritis with the characteristic morning stiffness. Steroid therapy was maintained after surgery.

DR. DANIEL BACHMAN (*Boston, Mass.*): We have also been interested in the problem of morning stiffness, and we have turned our attention to some of the normally occurring physiological rhythms in the body. One of the oldest and best known is the diurnal rhythm of urinary chloride excretion. During the day a normal individual excretes from two to three times as much chloride in the urine as during the night.

In fourteen patients with rheumatoid arthritis, we performed preliminary studies in which the chloride excretion in the urine was measured during the day

period 8 a.m. to 8 p.m., and during the night from 8 p.m. to 8 a.m. Urine was collected for six consecutive 12-hour periods.

Of the fourteen patients, six showed a reversal of the diurnal pattern, with a greater excretion of chloride in the urine during the night than during the day. Four showed what we have called suppression of the normal day-night pattern, in that there was approximately an equal amount of chloride excreted in the urine by day and by night. The remaining four patients showed normal rhythm.

We are not yet prepared to draw any conclusions concerning these preliminary observations. Extension of these studies should include control of factors such as the total amount and time distribution of chloride intake, the amount of physical activity, posture and whether the patient sleeps at night or lies awake. However, I think our findings are of interest in relation to the data presented in the preceding two papers.

DR. JAMES B. WYNGAARDEN (*Bethesda*, Md): Dr. Peterson and I have been interested in the problem of adrenal hydrocortisone production and have recently published data on the size and rate of turnover of the miscible hydrocortisone pool (Wyngaarden and Peterson, 1955). This study involved the injection of a small dose of labelled hydrocortisone and the measurement of the rate of change in specific activity of circulating hydrocortisone. Specific activity falls only by virtue of the addition of new, unlabelled hydrocortisone from the adrenal. It is not influenced by changes in the rates of degradation or excretion.

We have studied a few individuals at both 8 a.m. and near midnight, and found a decided decrease in rate of steroid production late in the day. Average adrenal production of hydrocortisone in the morning is equivalent to about 17 to 29 mg. hydrocortisone a day. In one individual, whose rate of hydrocortisone production was 1·22 mg./hr in the morning, a decline to 0·51 mg./hr was observed in the late evening.

We also used large doses of hydrocortisone and measured the rate of disappearance of hydrocortisone from the plasma. We find there is no appreciable difference in the rate of disappearance of the steroid in the morning or evening. Furthermore, the diurnal rhythm in the plasma level of hydrocortisone is reflected in a similar pattern of urinary steroid excretion except there is approximately a 2-hr lag.

Taking all these data into consideration, we believe diurnal variations result from variable rates of adrenal hydrocortisone production and have little to do with changes in excretion or metabolism rates.

DR. WALLACE GRAHAM (*Toronto, Canada*): Has Dr. Warren studied the morning stiffness problem in patients suffering from so-called fibrositis or psychogenic rheumatism.

DR. JOSEPH J. BUNIM (*Bethesda, Md*): Granted that patients with rheumatoid arthritis have stiffness in the morning, and granted that stiffness disappears several hours after a maximum level of hydrocortisone in the plasma is attained, are we warranted in regarding these two phenomena as cause and effect. The essayists imply that the 7 a.m. plasma peak dissipates, hours later, morning stiffness; but this still remains to be proved. Indeed, morning stiffness seems to coincide temporarily with the maximum plasma concentration of hydrocortisone.

DR. RICHARD D. MILLER (*Pasadena, Calif.*): I should like to add that these patients who underwent surgery had been observed constantly for 4 years before surgery, and that morning stiffness in these patients was very marked, and has now disappeared. This is not simply a matter of steroid levels after surgery.

DR. JOHN LANSBURY (*Philadelphia, Pa*): In trying to correlate morning stiffness with the ebb and flow of plasma hydrocortisone levels, we should not forget that patients who are subject to morning stiffness are also subject to recurrent stiffness after resting during the day. This diurnal "jelling" I look upon as "morning stiffness in miniature", and it does not appear to be correlated with plasma steroid levels; it may be that morning stiffness is likewise unrelated and is due, rather, to prolonged muscular and articular inactivity.

DR. ARTHUR A. HELLBAUM (*Oklahoma City, Okla.*): I speak as a member of a Pharmacology Department. Much of our activity at one time was devoted to the measurement of the blood levels of various chemicals and compounds. Many of us are now wondering about the significance of this type of measurement, and the same scepticism may carry over to the determination of blood levels in clinical laboratory procedures. Our students sometimes facetiously remark that "at least our patients die in electrolyte balance".

The type of work reported in the preceding papers is important and essential; but we must remember that the blood stream is but a highway of transport and that the concentration of the substances found there may or may not be related to the functional concentration or activities of these substances found at the beginning or end of their transportation in the blood stream.

DR. WARD: In answer to Dr. Graham's question, I can only say that, in our patients with psychogenic rheumatism, the levels at 8 a.m. corresponded very closely to those seen in normal individuals and in rheumatoid patients. As yet, we do not have a large enough series of "primary fibrositis" to comment.

We should like to study steroid concentrations at tissue level, but at present, we have no way of doing so.

DR. WARREN: Dr. Miller's report on the effect of adrenalectomy is fascinating and I would agree that it is quite possible that the stiffness is produced by some other mechanism than a disturbance in hydrocortisone metabolism.

Also in answer to Dr. Bunim, we did not think we could relate the presence or total absence of stiffness with hormonal levels in the group as a whole, because "normals" are insufficient controls, but we related the tendency for stiffness, already present, to increase and decrease with the rise and fall of corticoid levels in the preceding hours.

That also partially answers Dr. Lansbury's question. We agree that other factors, including physical immobility will produce variation in stiffness.

Dr. Bachman's report that the rheumatoid patients show a continued excretion of water and chloride at night may be explained by these high night time levels of cortisone that we have observed in many patients.

Quantitation of Activity, Spread, and Deformity in Rheumatoid Arthritis.* By JOHN LANSBURY, *Philadelphia, Pa.*

Since the aetiology of rheumatoid arthritis is unknown,

* (Based in part on data from twenty physicians cooperating with the CENTA programme in 1955.)

its severity, its course, and its response to therapy must be judged indirectly by its inflammatory manifestations. These may be articular, or systemic, or both. In order to test an index of the severity of rheumatoid "activity", serial observations must be recorded as the disease pursues a presumedly steady course between two identifiable points:

(1) The state when therapy is instituted,
(2) the state of full clinical remission.

The following indices of systemic rheumatoid activity declined in a regular manner as patients went into remission, and are therefore accepted as quantitative indicators of rheumatoid activity:

(1) Maximum 5-minute Cutler erythrocyte sedimentation rate.
(2) Degree of anaemia.
(3) Duration of morning stiffness.
(4) Daily aspirin consumption.
(5) Hours of activity before fatigue.
(6) Weakness of hand grip.

For various reasons, fever, rest pain, and abnormal serum proteins are unsuitable as indices.

The percentage values for gradations of each index are given in a Table. By averaging their sum one obtains an "Index of Rheumatoid Activity". Not more than 5 or 6 minutes is needed for gathering the basic data and making the calculation. Our results suggest that this index is sufficiently accurate both for clinical use and for the evaluation of therapeutic responses at the research level.

Joint findings may also be summed up and expressed in a single figure as a percentage of total possible involvement. Studies of the area of articulating surfaces of all peripheral joints are given in Tables. These areas are proportional to joint size, so that, by referring to them, it is possible to calculate the total "amount" of arthritis. (Further refinements, such as summing up degrees of joint inflammation and deformity, are also possible but are too time-consuming for routine use.)

Discussion.—DR. OTTO STEINBROCKER (*New York, N.Y.*): I think Dr. Lansbury is to be congratulated for the persistence and zeal with which he has attempted to find some method of measuring the activity and therapeutic response of patients with rheumatoid arthritis.

For many years I was interested in this subject, and I know it is a difficult and complicated one. The greatest pitfall, of course, is the attempt to quantitate subjective information. If the mathematical and calculus-like method he has devised can overcome the difficulties of quantitating much of this information, I think it should be very valuable.

I hope for his sake that before this study is completed—or possibly I should reverse it and say I hope for the patients' sake that by the time this method has been worked out, a truly specific therapeutic agent will become available. All these complicated indices then would hardly be necessary, because it will be very obvious, when we have such an agent, that the patients respond.

DR. LANSBURY: I should like to add that, although the reasoning behind this method may appear complicated, the application of the method is simple and requires only a few minutes of the clinician's time for recording the data and making calculations from Tables.

Furthermore, many of the items which we ordinarily think of as being "subjective" have been proved to be objectively determinable. For instance, I have found that most patients can give a very accurate account of the duration of morning stiffness. The constancy and reliability of this observation is proved by the regular rate of decline as patients go into remission, and the same thing may be said for the other observations.

DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa*): This ingenious method set up by Dr. Lansbury has a great deal of merit. I think all of us have been looking in vain for some years for a rapid and easy laboratory test which will show just how severe each case of rheumatoid arthritis is so that we can gauge its progress. Certainly we all know that the erythrocyte sedimentation rate is not such a test.

Until we do find such a test, or until we have a cure for this disease, we must develop some means of standardizing clinical evaluation.

Dr. Lansbury's method, which I have had the opportunity to try out, is the best I have seen.

DR. LANSBURY: I thank the discussors and again make a plea that many of you will try out the method. I shall be happy to send any interested clinicians the necessary details and Tables on request. In the meantime we plan to gather data on about thirty to fifty remissions so as to arrive at an authoritative statistical evaluation of each item and see how it should be weighted.

DR. JOHN H. VAUGHAN (*Richmond, Va.*): As I understand it, your 100 per cent. figure which refers to the average of a group of patients observed during a given period. The reference standard is your clinic patients or private patients. This means that, if we were to use your 100 per cent. value, then other studies of rheumatoid activity in a given patient would be referred to Dr. Lansbury's 100 per cent. In other words, it would show the activity of a given patient with respect to your average.

Would it be possible to work this thing out, so that we all started from a zero base line, and so achieve an absolute measure rather than one related to this particular series.

DR. LANSBURY: I should be delighted if those interested would send such information. To take another example, however, the data on which we based the average value for the Westergren sedimentation rate was furnished almost entirely by Drs Duff and Ziff.

I doubt whether securing data on, say, 1,000 cases would greatly alter our average values. Nevertheless, we shall try to collect these data by a "spot check" from a hundred clinics.

Significant Clinical Remissions in Rheumatoid Arthritis resulting from "Sensitivity" produced by Gold Salt Therapy. By THEODORE B. BAYLES and PAUL FREMONT-SMITH, *Boston, Mass.*

Since 1927 those concerned with gold salt therapy in rheumatoid arthritis have been debating the effect of this medicament. Many believe it will alter the course of rheumatoid arthritis and have speculated vigorously and unfruitfully on the therapeutic action of this heavy metal. Freyberg's excellent metabolic studies on gold salts in the body failed to reveal any common denominator. On identical amounts of gold one patient will do very well and the next will not. We recognize this dichotomy but still feel that gold salts are clinically useful.

Some years ago we first noted the marked clinical improvement in patients with definite gold "sensitivity" skin reactions. This paper presents 49 such patients, 35 females and fourteen males, between 20 and 78 years of age, who had 54 remissions. Rheumatoid arthritis had been present from 6 months to 30 years; 44 had 90 to 100 per cent. clinical improvement, and the remainder 50 to 90 per cent. The amounts of gold causing reactions varied from 100 to 1,600 mg. (average 600). The blood sedimentation index became normal within 2 to 4 weeks in 38 of 54 remissions. 27 remissions ended after 3 to 36 months (average 15). 27 are still in remissions after periods ranging from 3 months to 5 years. Changes in sedimentation rate and 17-hydroxysteroid excretion levels during "sensitivity", and preliminary data obtained with Dr. Joel C. Goldthwait on circulating antibodies, tuberculin- and immediate-type allergic skin reactions, gamma-globulin levels, and liver function tests during gold salt treatment and during "sensitivity" reactions were observed.

Discussion.—DR. RICHARD T. SMITH (*Philadelphia, Pa*): This particular phase of rheumatoid arthritis has been of great interest to us for some time. We tried to correlate, first of all, some data that might indicate why some patients respond and some do not.

On the basis of average doses of gold for different types of patients, we theorized that the accumulation level may make the greatest difference.

We have tried to put this together on a theoretical basis, considering that there is probably a 1 mg. per day excretion of gold. The curve showed rapid increase in the accumulation levels, showing a loss from one injection to another. There is a tolerance level, and if this is passed, we have evidence of toxicity or of a sensitivity reaction. There is also a minimum therapeutic level that varies considerably from patient to patient.

We see the amount of gold as actual gold, not as total dosage, and we toyed with the idea of giving gold up to the point of toxicity, since in the process a remission was bound to occur.

After watching many patients, we give a maintenance dose every 3 weeks in order to replace what is being excreted. A patient on a maintenance dose may from time to time begin to show evidence of exacerbation, and in such instances we give an immediate injection, and begin to raise the accumulation level. As the disease activity decreases they are put back on maintenance dosage. Some patients seem to be unable to tolerate a 3-weekly maintenance dose. Consequently, we have made a study of urinary excretion of gold.

After approximately 6 months of study, choosing patients with high and low tolerance levels (as low as 35 mg. gold salts), some in between, some just starting gold therapy, and some on maintenance dosage for 6 months, we begin to see a pattern that suggests that the variation lies not so much in a flexible tolerance level from patient to patient, as in the amount of gold excreted from day to day.

When we have a patient that develops a sensitivity reaction, we stop the gold, permit him to excrete enough to get over the toxic effect, and then reinstitute gold at a lower level that is tolerable to him, without giving time for an exacerbation to occur.

Apparently we need to approach the patient's tolerance level very closely to obtain a good remission. We should not force every patient to the toxicity level, but I do believe that most patients should have some gold given to them, and that a safe dosage system can be found.

DR. JOHN W. SIGLER (*Detroit, Mich.*): I should like to describe an experience we had in our clinic that varied slightly from these described by Dr. Bayles.

This patient had active rheumatoid arthritis and had received gold therapy at regular intervals for about 18 months. She was doing some spray painting in a closed room and shortly thereafter developed an extensive exfoliating dermatitis of the exposed areas of her skin. Her rheumatoid arthritis improved and, before her discharge from the hospital, she appeared to be in remission. This episode occurred 3 years ago and she is still in remission.

DR. RUSSELL L. CECIL (*New York, N.Y.*): All rheumatologists with extensive experience with gold know that gold dermatitis can bring about remission or near remission in these patients.

I always ask the patient whether he would rather have the very pruritic gold rash, or the pains of arthritis. More than one patient has said he preferred the arthritis. Be that as it may, this study is based on a nice observation, and I am glad to see it on our programme.

I should like to ask two questions: every now and then, we see patients who develop an exacerbation of pain and joint swelling with each injection of gold, so much so that after four or five injections we have to discontinue gold treatment entirely. Now, this exacerbation from gold salts was not accompanied by any sign of toxicity except a sharp increase in pain and swelling, and the patient had the impression (and so did I) that the exacerbation was related to the injection.

Secondly, having obtained good results with gold, it is very disappointing to see the almost inevitable return of arthritis a few months or maybe a few years later. The second course of gold is not so effective, and does not bring about a remission in so many cases as it did the first time. Has Dr. Bayles observed this, and if so, has he any explanation for it in relation to sensitivity?

DR. ROBERT C. BATTERMAN (*New York, N.Y.*): Is it necessary to treat rheumatoid arthritis patients with gold compounds to the point of toxicity? I know that, in my clinic and others, patients may obtain remission without the development of any toxic manifestion.

We have recently encountered several patients who have developed dermatitis under therapy, in whom the skin eruption was due to the sesame oil in which the gold compound was suspended. These patients were able to continue gold therapy by means of a compound suspended in olive oil. We do not wish to intimate that all dermatitis associated with gold therapy is related to sesame oil, but, in our experience, this makes up a good percentage of such patients.

DR. NATHAN R. ABRAMS (*Cincinnati, Ohio*): I have used gold sodium thiosulphate recently and have seen the same phenomenon, so it does not necessarily result from the oil used in some preparations. The remission does not occur with all types of reaction. For instance, I have seen no remission in one case who developed haematuria, one with optic atrophy (fortunately unilateral) and in cases with leucopenia. On the other hand, a remission did occur in a patient who developed purpura.

So far as the dermatitis is concerned, eosinophilia often develops before the dermatitis, and the remission occurs along with the eosinophilia, which may possibly be regarded as a warning signal.

In some of the patients who had rather severe reactions, the use of BAL has liberated gold, followed soon afterwards by exacerbation of the arthritis. I prefer to use as few drugs as possible for the reaction, but cortisone and ACTH have not seemed to interfere with the remission and I have occasionally used them for the dermatitis.

DR. RICHARD H. FREYBERG (*New York, N.Y.*): It is stimulating to note that interest in gold therapy continues. Dr. Bayles used the word "sensitivity" in quotes, which I think is quite appropriate. Most of the evidence to date supports the likelihood that dermatitis and other undesirable features—call them "toxicity" if you wish—are due to a hypersensitivity or to an antigen-antibody reaction rather than to cellular toxicity. However, this has not been proved. All of our efforts to identify the antigen causing dermatitis have failed. We tested the various inorganic gold salts that were used as therapeutic agents, and the gold-protein complex, which we found was the manner in which gold is transported in the blood; we were unsuccessful, but the evidence strongly suggests that this is indeed a sensitivity reaction.

Some Europeans favour much higher doses of gold than we have recently felt advisable. This is because they have seen, as Dr. Bayles's group has seen, that the benefit to the patient seems to be greater when certain of these undesirable reactions occur. Some people have even felt that the reactions are necessary to produce the benefit, but we do not think so.

Some of these "sensitivity phenomena" may develop in some patients, but remain subclinical, and certainly benefits occur in many patients without manifestations of toxicity.

Dr. Smith has mentioned the possibility of controlling the administration of gold salts by measuring the excretion of gold. I doubt whether this could be done. By chemical measurement of the concentration of gold circulating in the plasma or excreted in the urine, we were unable to find a "therapeutic level" above which administration is needed, or a "toxic level" below which troubles were avoided. Reasons for this may be the unpredictability of absorption and variability in the metabolism of gold from day to day; also the manifestations of toxicity are probably not exactly related to the amount of effective gold in the body. With improved methods for the quantitative determination of gold in the body fluids control of therapy may be more accurately attained.

The crux is that gold salt therapy is potentially valuable in the treatment of rheumatoid arthritis, but that we still do not know the mechanism whereby benefits are produced, or toxicity results.

DR. ROTHSTEIN (*Kansas City*): How do you manage dermatitis and what trouble do you have with depression of bone marrow in patients?

DR. BAYLES: I am delighted that so many people feel so strongly on this subject.

First, regarding Dr. Smith's remarks about the possibility of finding a level of serum gold which could be maintained with a favourable effect on rheumatoid arthritis, I am inclined to agree with Dr. Freyberg that there is no close correlation between the amounts of gold given and the therapeutic effect.

Dr. Sigler mentioned a case of exfoliative dermatitis thought to be due to paint who got complete remission of rheumatoid arthritis at the time of the dermatitis. Incidental dermatitis in patients receiving gold, such as dermatitis medicamentosa, nummular eczema, extensive seborrhoeic dermatitis, sunburn, and other irritations of the skin, do not cause remissions of rheumatoid arthritis, but I do not question his observation.

In answer to Dr. Cecil, some patients do complain of an exacerbation of the arthritic symptoms after the gold injection, but we do not let this alter our course of treatment. I agree that sometimes the second course of gold is less effective but in our series we had 54 remissions in 49 patients, so that remission occurred more than once with gold salt "sensitivity" in 5 cases.

I agree with Dr. Batterman that skin toxicity is not desirable and that many patients seem to get well without dermatitis.

Sesame oil can be a sensitizing agent. However, we have not been able to reach any logical conclusion from the cross skin sensitivity study comparing sesame oil alone and gold salts alone. I agree with Dr. Abrams that gold thiosulphate salt will bring about the same sort of response as we have described. Fortunately, we have never seen optic atrophy, but we do see nephritis or mild renal irritation due to gold, which is not associated, in my experience, with clinical remission of rheumatoid arthritis. When this occurs gold treatment should be stopped.

Dr. Freyberg has stimulated me in going ahead with this problem through the last 2 or 3 years. I agree with him that this reaction is probably due to "sensitivity" rather than to toxicity. I have not used higher doses than those mentioned because the only two deaths that we have had at the Robert B. Brigham Hospital or in my practice were of patients receiving more than 50 mg. a week. I think, if this therapeutic mechanism is going to operate, it will operate at a relatively safe level. Of the several hundred patients who have received gold, only two died, and they were receiving more than 50 mg. a week. This may be only a coincidence.

As to the question of handling the dermatitis, we have treated it in the classical fashion with B.A.L. (British Anti-Lewisite) and cortisone, usually in combination.

Adrenocortical Function in Patients receiving Long-Term Treatment with Cortisone. By ROBERT G. LARZELERE, EDWARD A. BARTHOLD, THOMAS V. FEICHTMEIR, FORREST M. WILLETT, and EPHRAIM P. ENGLEMAN, *San Francisco, Calif.*

22 patients were the subjects of this current study to determine the adrenocortical responsiveness to the stimulus of corticotropin after continuous therapy for 4 to 6 years with cortisone (daily doses ranging from 37·5 to 87·5 mg. or equivalent). This response was measured by significant increases in 24-hr excretion of urinary 17-ketosteroids and free corticoids, and by decrease in the number of circulating eosinophils.

According to predetermined and arbitrary criteria, all patients showed a definite response within 5 days. There was no correlation between the daily dose of cortisone or the duration of treatment and the adrenocortical response to corticotropin.

Fourteen of these patients had been subjects of such studies in previous years, and were now being studied for the third time. These successive tests, identical for each patient and unvaried from study to study, permitted a serial demonstration of adrenocortical response in each, and a comparison between patients receiving long-term treatment with cortisone. In these fourteen patients, no

consistent trend in adrenocortical responsiveness to corticotropin could be demonstrated.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md*): This study provides a sound basis for the practice of not interrupting the course of steroid therapy, or of administering from time to time ACTH to patients taking cortisone.

It would be helpful if the authors could clear up one more point for us. Is there a need for the administration of ACTH upon discontinuance of cortisone? One might reason that administering ACTH might suppress the endogenous secretion of corticotropin by the pituitary and may not, after all, be as helpful to the patient as it seems.

Did the authors compare recovery time (as measured by ACTH response) in patients receiving ACTH for several successive days after stopping cortisone with the recovery rate in patients who did not receive ACTH?

DR. LARZELERE: We have not made such a comparison, but it would be helpful to do so.

Effects of Hydrocortisone, Prednisone, and Prednisolone on Gastric Secretion in Humans. By W. H. KAMMERER and A. L. RIVELIS, *New York, N.Y.*

Studies were made of the effects of hydrocortisone, prednisone, and prednisolone on gastric secretion in individuals with rheumatoid arthritis (some of whom had had a peptic ulcer during steroid therapy), and in twelve volunteer non-arthritic subjects. Total secretion and viscosity determinations for a 2-hr period were made and hourly determinations of free HCl and uropepsin excretion for a 24-hr period were measured. The corticosteroids were then administered orally in varying doses and sequence for 5 or more days, after which similar aspirations and analyses were made; in some subjects the effect of concomitant antacid and anticholinergic agent administration was also studied.

In six subjects (all females) receiving hydrocortisone and prednisone alternately, there was an average rise of 10 units of free HCl secretion over basic levels. Total 2-hr secretion was increased and viscosity slightly lowered after administration of the steroids. No significant change in uropepsin excretion occurred.

Similar changes were not observed in six volunteers (4 males and 2 females) receiving prednisolone, but this may have been due to a variable in the sample. Neither the dosage of corticosteroid used (varying from 7·5 to 15 mg. prednisone and prednisolone and 20 to 60 mg. hydrocortisone daily), nor the sequence in which the steroids were administered appeared to have any consistent effect upon the results. Concomitant administration of antacids and anticholinergic agents resulted in a significant decrease in the level of free HCl.

The results of these studies do not indicate changes in the secretion of free HCl or pepsin that appear to be of any significance in the genesis of peptic ulcer in subjects receiving corticosteroids.

Discussion.—DR. JAMES H. BARR, JR. (*Pittsburgh, Pa*): Some time ago, not long after prednisone was introduced, we became impressed with the relatively high incidence of dyspepsia. This latter term was used to include symptoms ranging from mild gaseous distension to frank ulcer pain.

We, therefore, undertook a study in which *x*-ray examination of the upper gastro-intestinal tract and gastric analyses (Ewald meal) were performed on six rheumatoid arthritics before and after prednisone therapy, and on ten rheumatoid patients after the institution of prednisone therapy.

Of the group of six in which the studies were done before and after therapy, the Ewald gastric analyses included pH, and free and total acid measurements. In five of the six cases studied, there was an increase in free and total acidity with a drop in *p*H values. This increase was statistically significant, but was not as high as those usually observed in patients with peptic ulcer. None of these five patients developed peptic ulcer, the sixth patient did so.

In the group of ten patients studied after the start of predisone therapy, *x*-ray examination revealed two duodenal ulcers (niches) and one hiatal hernia with bleeding. On 30 to 40 mg. prednisone daily and a strict physiological antacid regimen, one ulcer healed, and one decreased in size by 75 per cent., while the bleeding from the hiatal hernia stopped.

One of our patients was a 58-year-old white male with long-standing rheumatoid arthritis. He was the only one of the six patients studied before and after therapy who developed a frank duodenal ulcer. His response to an Ewald test meal and a histamine injection was entirely normal before the onset of therapy. Hydrocortisone, 45 mg. daily, did not increase gastric acidity significantly although a duodenal ulcer niche was found by *x*-ray. Prednisone, 40 mg. daily, did increase acidity, but the ulcer crater decreased in size by at least 75 per cent. and gastric symptoms disappeared. He was on a rigid ulcer regimen during this period of prednisone therapy. The dosage of prednisone has since been reduced to 10 mg. daily, and the duodenal ulcer is now completely healed as indicated by *x*-ray examination and clinical findings.

I should like to emphasize that, though prednisone may increase gastric acidity as shown by the response to an Ewald meal, we have seen no consistent correlation between this increased acidity and the presence of peptic ulcer. We have, indeed, found, as has Dr. Kammerer, that when prednisone therapy is essential for patients with rheumatic disease who have peptic ulcer, a strict physiological antacid regimen will often permit the lesion to heal.

DR. DAVID H. NEUSTADT (*Louisville, Ky*): I have had the opportunity of observing a total of 47 patients with rheumatoid arthritis who have received either prednisone or prednisolone for one year or more. So far, we have been fortunate in not having any gastro-intestinal catastrophes, though some form of gastro-intestinal symptoms did occur in fifteen patients (29·7 per cent.). Upper gastro-intestinal *x*-ray studies were not done routinely, but radiological studies of the gastro-intestinal tract were carried out in all patients who developed any gastro-intestinal symptoms. No duodenal ulcers were found, but gastric ulcers were found in two patients (4·2 per cent.). In one of the latter, a female, the drug was withdrawn and the ulcer healed with appropriate therapy. The other patient, a male, developed a large ulcer on the greater curvature after 4 months of steroid treatment. An ulcer regimen was instituted and the prednisone was continued without altering the dosage

The ulcer symptoms abated and its healing was followed by serial *x*-rays until after a month it was completely healed.

I should like to comment briefly on the recommendation of some workers that every patient given the new steroids should routinely receive concomitant antacid therapy prophylactically. I doubt that this would be sufficient to prevent the occurrence of ulcer disease, and think that this procedure may do harm by masking or suppressing the usual ulcer symptoms, so that the clinician and patient are not sufficiently aroused to request *x*-ray study. Then, instead of pain giving the initial signal, the patient may be introduced to his new malady by a more serious manifestation, such as sudden gastric haemorrhage or perforation. If my patient is developing an ulcer, I want to know about it as soon as possible.

Of incidental interest to this subject are some recent studies done in the Gastro-enterology Department of the University of Louisville. Cortisone was administered intramuscularly 50 mg. daily to two Dragstedt-pouch dogs for 2-3 months, after a control period of the same interval. There was no increase in output or volume of HCl. This is in contrast to work by others with ACTH in dogs, in which HCl output was stimulated in the presence and absence of both the vagal and antral mechanisms. Although these results are of limited clinical interest owing to differences in pharmacological response, they demonstrate the absence of influence by a profoundly potent steroid in the same species, when the action of both is considered so similar in humans, and may suggest some other mechanism of action as related to production of HCl in the gastro-intestinal tract.

Having previously participated in studies of gastric secretion in humans, I know the difficulties involved. I am sure the authors will not consider it amiss if I recall some of the factors that must be taken into consideration in attempting to interpret the results of gastric analyses.

(1) Spontaneous fluctuation of basal gastric secretion, even in experimental conditions, in the same patient on different days.
(2) Psychological effect of passage of tube.
(3) Psychic stimulations to gastric secretion produced by sight, smell, food, or suggestion during tests.
(4) Possible loss of gastric juice through pylorus or regurgitation of bile into stomach.

I should like to know whether any special techniques for overcoming or avoiding any of these pitfalls have been evolved.

Lastly, of course, definitive analysis is greatly handicapped by our lack of knowledge of all the factors contributing to the formation of peptic ulcer.

Psychosomatic Study of Children with Rheumatoid Arthritis. By GASTON E. BLOM and ROBERT T. LONG, *Boston, Mass.*

In this paper we report on a continuing study of emotional factors in juvenile rheumatoid arthritis. Our study is based on clinical data obtained in psychiatric interviews with 58 patients (39 girls and 19 boys), ranging in age from 1½ to 16 years of age. Common features were noted in emotional factors related to onset and recurrence, past historical events appearing to have a determining influence on the personality characteristics of mother and child, and in personality aspects of mother and child.

For further clarification of significant emotional factors, data from rheumatoid arthritis cases have been compared with similar data from other disease groups (asthma). Certain emotional factors showed a primary relation to rheumatoid arthritis in children, and were differentiated from secondary emotional factors derived from illness and hospitalization.

Discussion.—DR. ARTHUR I. SNYDER (*New York, N.Y.*): I should like to ask for more information about the selection of the patients for your study. As I recall Dr. Ludwig's study, the results of which you compare with yours, his patients were referred because of psychological symptoms and had rheumatoid arthritis in addition.

DR. BLOM: Our series of cases comprised every patient that was admitted to the hospital for rheumatoid arthritis, and also every case seen in the out-patient department. At the beginning of the study we did see cases referred to us because of psychological problems, but since that time the greater number of our series was picked up routinely by the research team.

DR. SIDNEY COBB (*Pittsburgh, Pa*): I should like to congratulate Dr. Blom on what I think is magnificent methodology in approaching a problem which we all observed, but which we have not been able to isolate in our usual clinical studies, nor in our epidemiological studies to date.

DR. JOHN LANSBURY (*Philadelphia, Pa*): I have listened with great interest to this excellent paper. I am very much struck with the relationship between emotional upheavals and variations in the severity of disease and onset of disease in adults.

One of the things, however, which always puzzles me when we have psychosomatic discussions, is that the type of personality or emotional dynamics always sounds the same to me. We have aggression, throttled hostility, desires to kill the mother, all present in a variety of otherwise unrelated diseases, such as ulcerative colitis, peptic ulcer, or hypertension.

I should like to ask whether the speaker thinks there is a specific psychodynamic pattern related to arthritis or whether we are simply seeing an excessive amount of "negative energy" or "negative feeling", which can occur in *any* psychodynamic situation.

DR. BLOM: We do not believe in the personality type concept regarding the relationship of emotions to psychosomatic disease. Rather, we think there are psychological conflicts that are characteristic.

This group of patients, has some emotional similarity to ulcerative colitis patients and others with psychosomatic conditions. Our interest, however, is that there are significant differences, too, and we want clearly to differentiate these psychosomatic diseases if we can. We are impressed with the different ways these patients deal with similar situations of emotional conflict.

Synovial Lesions in Progressive Systemic Sclerosis (Diffuse Scleroderma). By GERALD P. RODNAN, ROGER L. BLACK, and JOSEPH J. BUNIM, *Pittsburgh, Pa*, and *Bethesda, Md.*

Arthritic symptoms are recognized to be of frequent occurrence in patients with progressive systemic sclerosis, often preceding the cutaneous and visceral manifestations of the disease. In an effort to learn more concerning

the nature of this joint involvement, synovial biopsies have been obtained from a suprapatellar bursa of thirteen consecutive patients with histologically confirmed diffuse scleroderma.

Evidence of visceral involvement was present in all but two of the patients at the time of the synovial biopsy. The synovium was found to be normal in the three patients without arthritic complaints. Ten patients in whom joint pain, swelling, and stiffness played a prominent role in the disease picture were found to have objective evidence of polyarthritis and markedly abnormal biopsies. The synovial lesions included focal aggregations of lymphocytes and plasma cells, villous hypertrophy, loss of synoviocytic lining, focal fibrosis, and sclerotic and perivascular inflammatory changes involving the smaller blood vessels. In four patients of this group. There was dense fibrosis of the synovium and the cellular infiltrations were less marked.

X-ray examination of affected joints disclosed narrowing of joint spaces and varying degrees of osteoporosis, but no destruction of bone. Sheep cell agglutination reaction was negative in nine patients and only slightly elevated in two. The clinical evidence suggests that this form of arthritic disease is distinct from rheumatoid arthritis and can be considered an integral feature of progressive systemic sclerosis.

Relation of Symptoms to Osteo-Arthritis. By S. COBB, W. R. MERCHANT, and T. RUBIN, *Pittsburgh, Pa.*

Over half of the persons we have seen in our population study, with marked radiographical evidence of osteo-arthritis failed to report any pain at the relevant sites. Similar findings have long disturbed the thoughtful clinician as he makes a diagnosis of degenerative joint disease. This has led us to investigate the concomitants of pain in osteo-arthritis.

In the course of our examination of 478 individuals selected at random from the Arsenal Health District of Pittsburgh, we found that morning stiffness is more closely associated with joint pain than are degenerative changes visible by *x* ray. This is most striking for the hands and wrists but is also true for the knees. When we limit our study to people with marked degenerative changes, we find that the greater is the amount of pain or swelling, the greater is the probability of having morning stiffness. Furthermore, we find that of these persons with marked degenerative changes, about 30 per cent. have pain and only 5-10 per cent. have pain without morning stiffness.

This strong association between morning stiffness and the presence of symptoms in those with *x*-ray evidence of osteo-arthritis arouses our curiosity, for it is well known that there is a marked association between morning stiffness and rheumatoid arthritis. This is a subject worthy of further investigation.

Pathogenesis of Osteo-arthritis of the Hip. By GOLDEN SELIN and HENRY JAFFE, *New York, N.Y.*

The natural progression of degenerative joint disease at the hip was followed in its various stages and phases from the earliest lesion of fibrillation to the advanced changes. The nature and genesis of the pathological involvement, and its peculiarities and complications were illustrated by sections of femora, and the corresponding acetabular structure and pelvic bones removed during surgery or at autopsy. The thesis that osteo-arthritis is a disease of the acetabulum as well as of the femoral head, and the need for measures based on such a total concept were illustrated by the pathological alterations. The relationship of these observations to degenerative articular disease was discussed.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): I cannot let the chance pass of saying what a splendid presentation this was. It clearly summed up years of experience and observation. I should like to offer my personal thanks to Dr. Selin.

Experience with a "Back to Work" Programme for Physically Handicapped Arthritics. By MR. MARTIN ACKER and DR. ROBERT H. MANHEIMER, *New York, N.Y.*

A total of 212 arthritics was referred to a vocational rehabilitation programme in 30 months, 159 cases, including 62 (39 per cent.) who had been returned to gainful employment, being closed by March, 1956.

The vocational rehabilitation programme includes:

(1) Screening and evaluation, to select suitable clients;
(2) Vocational counselling, to identify the patient's skills, aptitudes, limitations, and motivations, design his rehabilitation, and supply guidance throughout the course.
(3) Vocational training;
(4) Help in finding a suitable job.

Men and women were referred in almost equal numbers. A slightly higher proportion of men returned to work. Half the patients were aged from 40 to 59; 46 per cent. in this age group and one-fourth of those aged 60 or more found employment. The major diagnostic categories were:

Rheumatoid arthritis	94
Osteo-arthritis	21
Spondylitis	16

Rheumatoids returned to work at the same rate as the whole group. Disability varied widely but even severe impairment did not necessarily preclude vocational rehabilitation.

The patients' ability to return to work in relation to the duration of illness was as follows:

Duration of Disease (years)	*Percentage returning to Work*
1-4	38
5-9	47
10-19	44
20-	30

At referral, 105 patients were unemployed; 39 had never worked; and fifteen faced problems on their jobs caused by arthritis. The 62 who returned to work included 44 unemployed patients, eight without employment history, and ten who were working at referral.

Vocational rehabilitation required from a few weeks to over a year, depending on the patient's disability, skills, experience, and motivation.

Discussion.—DR. OTTO STEINBOCKER (*New York, N.Y.*): I know the hour is late but I must say a few words about this projection my own behalf and on that of my colleagues who use it in New York. This is a remarkable recent development in the management of disabled patients. It represents a step forward for a group of individuals who need to progress beyond the small amount of help we could give them.

The possibilities which Mr. Acker and his project have opened up for them are beyond anything that we could have imagined before this work was instituted.

DR. H. S. ROBINSON (*Vancouver, Canada*): We have had a project going for some years in Vancouver, trying to return patients to work. These are patients who initially, are put in the rehabilitation centre. While they are there, they have vocational guidance, and so forth, and we have found it a successful and useful endeavour.

Could you tell me whether you have a work tolerance programme in the rehabilitation centre carried on by your occupational therapy department?

MR. ACKER: Yes. The patients in the "Back to Work" project are ordinarily people whose work tolerance had reached the maximum of about eight hours a day before they were accepted for the project. Patients are accepted whose work tolerance is less than 8 hours if it is anticipated that they may reach full tolerance when the vocational rehabilitation programme is completed (usually 9 to 12 months). There is a work tolerance project at the Institute for the Crippled and Disabled which selects patients for referral to a training programme such as this one.

DR. WILLIAM H. KAMMERER (*New York, N.Y.*): Can Mr. Acker give us any idea of the cost per patient for this rehabilitation.

MR. ACKER: That is an extremely difficult estimation to make. The Institute for the Crippled and Disabled is a multi-purpose centre which is used extensively for teaching and research, as well as for direct services to patients. Columbia and New York Universities use it for training occupational and physio- therapists and other training programmes also operate there. I doubt whether the cost of this particular unit has been determined. I suspect that for training, the cost is relatively high, but it would not be so high if the Institute had not so many other functions. I am not in a position to give you a detailed cost breakdown.

DR. WILLIAM H. KAMMERER (*New York, N.Y.*): "Relatively high" means different things to different people. "Relatively high" to me is $10. I wonder if you have any idea what "relatively high" is.

MR. ACKER: It really is extremely difficult to give you a dollar-and-cent figure. The Institute operates on an annual budget of about half-a-million dollars for something around 1,470 patients—I haven't the exact figures. We can break it down from there, but it does not mean very much in terms of cost per individual patient for direct services to the patient.

It would not be satisfactory to set up a programme based on individual costs.

Course of Systemic Lupus Erythematosus during Long-Term Maintenance Therapy. By MORRIS ZIFF, PAUL ESSERMAN, and CURRIER MCEWEN, *New York, N.Y.*

The course of systemic lupus erythematosus as currently observed and treated has changed since 1949. Two new influences have modified the observed life history of the disease; the introduction of hormonal therapy, and the discovery of the L.E. cell test as a criterion for diagnosis. The L.E. cell test has led to the diagnosis in patients with milder forms of the disease than were heretofore recognized; treatment with hormones has lengthened life. It is important, therefore, to review our knowledge of the life history of lupus erythematosus in the light of these new influences.

This investigation follows the course of 24 patients for up to 4 years. All but one were treated with steroids, and thirteen received combined treatment with steroids and chloroquine or Atebrin. The course of the majority of the patients receiving combined therapy has been relatively benign. All but one are alive and controlled on moderate maintenance dosage. The average duration of therapy was 18 months.

Renal function, as measured by dye excretion and endogenous creatine clearance tests, appeared to diminish slowly, if at all, in most patients during the period of observation. The degree of albuminuria tended to fluctuate significantly, and protein often disappeared from the urine for months.

Psychosis, which was present in eight patients, improved with administration of steroids. Relapse of activity, when it occurred, appeared to follow a characteristic pattern for each patient. Close supervision of maintenance therapy appeared to diminish the frequency and severity of relapses.

Sensitized sheep cell agglutination tests on the euglobulin fraction, carried out in sixteen patients, were positive in five. In these, the character of the joint involvement resembled that seen in rheumatoid arthritis.

The course of the erythrocyte sedimentation rate, C-reactive protein test, albumin/globulin ratio, sensitized sheep cell agglutination titre, serological test for syphilis, and L.E. cell test during therapy was charted.

Mucocutaneous Lesions of Reiter's Syndrome. By MAX M. MONTGOMERY, ROBERT M. POSKE, EVAN M. BARTON, DONALD T. FOXWORTHY, and LYLE A. BAKER, *Chicago, Ill.*

The incidence of mucocutaneous lesions in patients with Reiter's syndrome treated during an 8-year period at the Hines Veterans' Administration Hospital was found to be greater than that reported in other series. Thirty of the 38 patients presented perimeatal erosions and/or balanitis circinata lesions (80 per cent.). 23 patients had both lesions; four of the remaining seven had perimeatal erosions; three had balanitis circinata alone.

In addition, fourteen of these thirty patients (37 per cent. of the 38), had painless oral, pharyngeal, or glossal mucous membrane lesions. A number of others had diffuse injection of the palate and pharynx and darker red mucosal areas which possibly represented the terminal stage of previous lesions. These were not included.

Keratodermia blennorrhagica-like lesions, the keratosis of Reiter's syndrome occurred in eleven of the thirty patients with mucosal lesions (30 per cent. of the 38), nine

presented hard nodular hyperkeratotic lesions, and two had soft parakeratotic patches.

We believe that mucocutaneous lesions may be as important in establishing the diagnosis of Reiter's syndrome as are the non-specific urethritis or conjunctivitis. In equivocal cases, when urethritis and/or conjunctivitis have not been observed or well documented, the mucocutaneous lesions, known to appear 4 to 6 weeks after the onset, may be diagnostic. In the endemic form, the triad of Reiter's syndrome might better be considered a tetrad, consisting in its complete form of urethritis, conjunctivitis, arthritis, and mucocutaneous lesions.

* * * *

Report of Committee on Diagnostic Criteria

GRANVILLE A. BENNETT SIDNEY COBB
RALPH JACOX RALPH JESSAR
MARIAN W. ROPES (*Chairman*)

Proposed Criteria for the Diagnosis of Rheumatoid Arthritis. Presented by Marian W. Ropes, *Boston, Mass.*

In a disease of which the aetiology is not known and in which there is no proof of diagnosis, diagnostic criteria will assist in securing uniformity in the cases included in any discussion, study, or report of the disease, whether it be concerned with prevalence, incidence, manifestations, course, or treatment.

The classification of rheumatoid arthritis in three groups seemed the most useful way to begin.

(1) The definite group, in which there is almost no question that every patient has rheumatoid arthritis;

(2) The probable group, in which it is highly probable that every patient has rheumatoid arthritis;

(3) The possible group, which will contain chiefly patients with rheumatoid arthritis but may also include some with other diseases.

It is apparent that the first two groups will be used in any study of the characteristics, course or treatment of rheumatoid arthritis.

Since no absolute criteria applicable to all cases could be set up, the most satisfactory approach was to determine the characteristics—such as morning stiffness, soft tissue swelling, typical *x*-ray changes, and symmetry of involvement—which, if present in adequate number, would establish the diagnosis. Because of the similarity to the clinical findings in various other diseases it was necessary to list evidence of these diseases, which, if present, would exclude the patient from the groups diagnosed as rheumatoid arthritis. In some cases it is possible that patients with one of these other diseases, for instance one of the generalized connective tissue diseases other than rheumatoid arthritis or other rheumatic disease such as gout, may be thought to have rheumatoid arthritis also (as a patient with a history suggesting rheumatic fever and with physical findings of mitral and aortic valvular disease but also with a recent history and findings of definite rheumatoid arthritis). However, in such a situation, it seems wisest not to include the patient in a study of rheumatoid arthritis but to classify him separately and compare as desired. On the other hand, patients with rheumatoid spondylitis (*x*-ray changes in sacro-iliac joints or persistent limitation of motion of any region of the spine), or with psoriasis, ulcerative colitis, or onset under the age of 12, are to be included in the rheumatoid groups, if they satisfy the criteria, but should be listed separately and the findings given separately.

Rheumatoid arthritis is a systemic disease occurring at all ages, more frequently in women than men. Many of the signs and symptoms are entirely non-specific and of no value in differential diagnosis, and are therefore not included in the criteria. The majority of these are the indications of the systemic involvement in the disease—fatigue, anorexia, weight loss, fever, vasomotor symptoms, paresthesias, lymphadenopathy, anaemia, leukocytosis or leukopenia, and increased concentration of total globulins or of α and γ globulins and fibrinogen and decreased concentration of albumin in the blood. Similarly, many of the findings are evidence of skeletal tissue inflammation and its sequelae—muscle atrophy, skin atrophy, pigmentation, tenosynovitis, and palmar fascia thickening; these are also non-specific and are not included. Pericarditis, myocarditis, and pleurisy have been omitted from the criteria because they are more frequent in other diseases than in rheumatoid arthritis and would tend to lead to the wrong inclusion of many patients. In general, patients with rheumatoid arthritis can be diagnosed by the criteria as they stand at the time they develop any of the above manifestations.

The criteria for the diagnosis of *definite* and *probable* rheumatoid arthritis have been made relatively rigid, since cases included in these groups will be used for study of the disease and often as a basis for statistical conclusions as to prevalence, incidence, characteristics, course, and treatment. However, it was considered important not to make the criteria so strict that only far-advanced so-called "typical" cases, or cases of long duration could be included. The required duration of joint symptoms (6 weeks in

definite rheumatoid arthritis and 4 weeks in probable rheumatoid arthritis) was made as short as possible without risk of making the diagnosis insecure. The duration tends to exclude the majority of cases of infectious and traumatic arthritis. Similarly, involvement of a minimal number of joints was required, two joints being sufficient if enough of the other criteria are present. The objective evidence of joint involvement, such as swelling, must be observed by a physician, but all observations need not necessarily be made by the same physician. When two joints are not involved simultaneously, they may satisfy the criterion of joint involvement if there is no interval free of joint symptoms of more than 3 months. If a longer interval has occurred, the possibility of the existence of two separate types of joint disease becomes greater. *X*-ray changes due to degenerative joint disease will not satisfy the criterion, but the presence of such *x*-ray changes will not exclude patients from the groups of rheumatoid arthritis. This proviso will lessen the likelihood that patients with mild rheumatoid arthritis who also have degenerative joint disease will be excluded from the rheumatoid groups. The nature of the mucin precipitate from synovial fluid was thought to be the most easily determined and most characteristic finding in rheumatoid fluids. Other abnormalities, especially increased activity of aminotripeptidase or betaglucuronidase, will add weight to the diagnosis but are not included as required criteria.

The criteria for the diagnosis of *possible* rheumatoid arthritis are much less rigid. In this way it will be possible to pick up very early, mild, or atypical cases which might otherwise not be noted and which can be followed profitably to learn more of the course and nature of the disease. It is realized that, of necessity with such liberal criteria, some patients who do not have rheumatoid arthritis will be included in this group. However, the errors in diagnosis will, in most cases, become apparent as the group is followed, and the patients included in the "possible" group cannot be used for conclusions as to the characteristics or results of treatment of the disease.

The committee suggests that, if these criteria are acceptable, they be published now with the stipulation that they be reviewed and revised in 1959 or earlier if advisable.

PROPOSED CRITERIA FOR RHEUMATOID ARTHRITIS MAY, 1956

Rheumatoid arthritis is a systemic disease of unknown aetiology occurring at all ages, more frequently in women than men. It has been classified in these criteria in three groups—definite, probable, possible. The definitions of these states as outlined below are to be used for the identification and classification of cases for clinical study and treatment and for reporting the prevalence and incidence of the disease. The value of the criteria lies in establishing the findings necessary to allow inclusion of a patient in one or another of the groups. In this way only is it possible to obtain relative uniformity in the cases included (for discussion, study, or reporting) in any group of patients with rheumatoid arthritis (definite, probable, or possible) and to allow the comparison of a group from one source (physician or clinic) with those from other sources.

When these definitions are used, patients with rheumatoid spondylitis (*x*-ray changes in sacro-iliac joints or persistent limitation of motion of any region of the spine), or with psoriasis, or with ulcerative colitis, or with onset under the age of 12 should be included if they satisfy the criteria, but they should be listed separately and the findings given separately.

Any one of the exclusions listed in Section II will rule out the diagnosis of rheumatoid arthritis (definite, probable, or possible).

SECTION I

(A) *Definite Rheumatoid Arthritis.*—This diagnosis requires five of the following criteria and the total duration of joint symptoms must be at least 6 weeks.

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid—not just bony overgrowth) in at least one joint (observed by a physician).
4. Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms may not exceed 3 months).
5. Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of mid-phalangeal metacarpophalangeal, or metatarso-phalangeal joints is acceptable without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules (observed by a physician) (over bony prominences, on extensor surfaces, or in juxta-articular regions).
7. *X*-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes) —degenerative changes do not exclude patients from the group of rheumatoid arthritis.
8. Positive sheep cell agglutination (Rose and Ragan, or Heller test) or positive streptococcal agglutination test.
9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
10. Characteristic histological changes in synovial membrane with three or more of the following:
    marked villous hypertrophy;
    proliferation of superficial synovial cells often with palisading;

marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form "lymphoid nodules";
deposition of compact fibrin, either on surface or interstitially;
foci of cell necrosis.

11. Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly peri-vascular.

(B) *Probable Rheumatoid Arthritis.*—This diagnosis requires three or four of the above criteria and the total duration of joint symptoms must be at least 4 weeks.

(C) *Possible Rheumatoid Arthritis.*—This diagnosis requires two of the following criteria:

1. Morning stiffness.
2. Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for 3 weeks.
3. History or observation of joint swelling.
4. Subcutaneous nodules (observed by a physician).
5. Elevated sedimentation rate or C-reactive protein.
6. Iritis.

SECTION II. EXCLUSIONS

1. The typical rash of *disseminated lupus erythematosus* (with butterfly distribution, follicle plugging, and areas of atrophy).
2. High concentration of *lupus erythematosus cells* (four or more in two smears prepared from heparinized blood incubated for not more than 2 hrs).
3. Histological evidence of *periarteritis nodosa* with segmental necrosis of arteries associated with nodular leukocytic infiltration extending perivascularly and tending to include many eosinophils.
4. Persistent muscle swelling of *dermatomyositis.*
5. Definite *scleroderma* (not limited to the fingers).
6. A clinical picture characteristic of *rheumatic fever* with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules or erythema marginatum or chorea. (An elevated antistreptolysin titre will not rule out the diagnosis of rheumatoid arthritis.)
7. A clinical picture characteristic of *gouty arthritis* with acute attacks of swelling, redness, and pain in one or more joints, especially if relieved by colchicine.
8. Tophi.
9. A clinical picture characteristic of *infectious arthritis* of bacterial or virus origin with:
   an acute focus of infection or in close association with a disease of known infectious origin;
   chills;
   fever;
   acute joint involvement, usually migratory initially (especially if there are organisms in the joint fluid or response to antibiotic therapy).
10. *Tubercle bacilli* in joints or histological evidence of joint tuberculosis.
11. A clinical picture characteristic of *Reiter's syndrome* with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.
12. A clinical picture characteristic of the *shoulder-hand syndrome* with involvement of one shoulder and the hand on the same side with diffuse swelling of the hand followed by atrophy and contractures.
13. A clinical picture characteristic of *hypertrophic pulmonary osteo-arthropathy* with clubbing of the fingers and/or hypertrophic periostitis along the shafts of the long bones, especially if an intra-pulmonary lesion is present.
14. A clinical picture characteristic of *neuro-arthropathy* with condensation and destruction of the bones of involved joints and with associated neurological findings.
15. *Homogentisic* acid in the urine detectable grossly with alkalinization.
16. Histological evidence of *sarcoid* or positive Kveim test.
17. *Multiple myeloma* as evidenced by marked increase in plasma cells in the bone marrow, or Bence-Jones protein in the urine.
18. Characteristic skin lesions of *erythema nodosum.*
19. *Leukaemia* or *lymphoma* with characteristic cells in the peripheral blood, bone marrow, or tissues.

Discussion.—DR. ARTHUR W. BAGNALL (*Vancouver, B.C.*): This is a most excellent effort, although it seems unlikely that everyone will ever agree completely on one set of criteria. However, there is just one point I should like to inquire about and that is the pronouncement that "Any interval free of joint symptoms may not be more than 3 months". I wonder if that is wise. I have a private practice and clinic practice as well, and I am accustomed to seeing in my consulting room quite a few cases of undoubted rheumatoid arthritis who have a history of periods of freedom from joint involvement for much more than 3 months. This is what I call the "schnorkel" type of rheumatoid disease, because it only comes to the surface every now and then.

DR. ROPES: This question indicates how hard it is to express the criteria. We think any interval between the two individual involved joints should not be more than 3 months. Surely, there may be an interval free from all symptoms, and then episodes of joint involvement. However, it was our feeling that, if a patient had traumatic arthritis for one year, and 8 months later a second joint was involved and had at that time just enough other evidence to include him in the category of rheumatoid arthritis, it would be unwise to regard those two joints, in which the onset was separated by 8 to 12 months, as two joints involved in the disease. The criterion should obviously be re-worded.

* * *

PANEL DISCUSSION

Pathogenesis, Diagnosis, and Treatment of Gout

(*Moderator: Dr. Alexander Gutman*)

MODERATOR GUTMAN: I have asked Dr. Stetten to cover questions dealing with the intermediary metabolism or formation of uric acid and/or other purines.

Coming to the details of management, Dr. Charley Smyth will discuss acute gouty arthritis, and Dr. Elmer Bartels will consider the vexing problems of the prevention and treatment of chronic gouty arthritis.

Each panelist will present his particular subject, and this will be followed by a discussion of larger questions which are controversial or confusing. I shall refer to your specific questions that we have at hand, and that I hope will come to us in the course of this discussion.

(1) Current Status of Purine Biosynthesis—An Interim Report. By DEWITT STETTEN, JR., *Bethesda, Md*: As a result of the efforts of a large number of investigators working in various laboratories, considerable advances have been recorded in the understanding of the biosynthesis and metabolism of purines in the past few years. No attempt will be made here either to review the literature or evaluate the contributions from these many sources. Rather I shall attempt very briefly to integrate the various reported reactions, and to give a picture of how the purine nucleus is assembled, and what may happen to it in the animal body.

We may start our considerations with 5-phosphoribosyl pyrophosphate (Kornberg, Lieberman, and Simms, 1954). In this molecule, the anomeric carbon atom 1 is activated by the pyrophosphate group which, in the presence of glutamine, is replaced by an amino group (Goldthwait, 1956), as shown in Fig. 1.

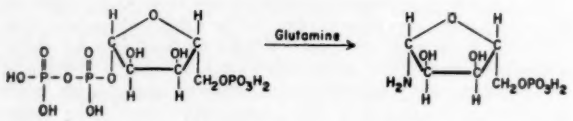


Fig. 1.

5-phosphoribosylamine is thus produced with glutamic acid and pyrophosphate as by-products. Glycine now reacts with phosphoribosylamine to give glycinamide ribotide (Goldthwait, Greenberg, and Peabody, 1955), as shown in Fig. 2.

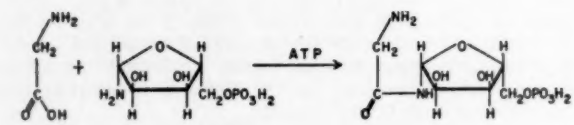


Fig. 2.

Energy for this process is supplied by adenosine triphosphate.

Glycinamide ribotide is next formulated on its alpha nitrogen atom, the one-carbon addend arising from the beta carbon atom of serine, transfer being effected by some derivative of folic acid (Warren and Flaks, 1956), as shown in Fig. 3.

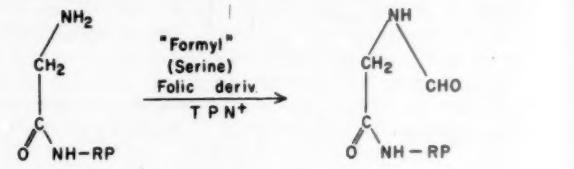


Fig. 3.

In this and subsequent figures, the ribose-5-phosphate substituent is designated simply as —RP.

The next step appears to involve transfer of a nitrogen, again from glutamine, converting the glycin*amide* portion of the molecule to glycin*amidine* (Levenberg and Melnick, 1956). This is followed by cyclization, with completion of the five-membered imidazole ring of the purine nucleus (Fig. 4).

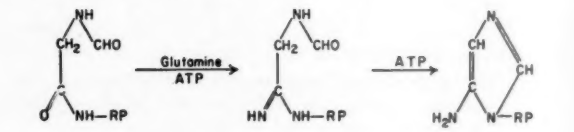


Fig. 4.

5-aminoimidazole ribotide now acquires a carbon atom at position 4, arising from bicarbonate, to which a nitrogen atom, derived from aspartate, is next attached (Lukens and Buchanan, 1956), see Fig. 5.

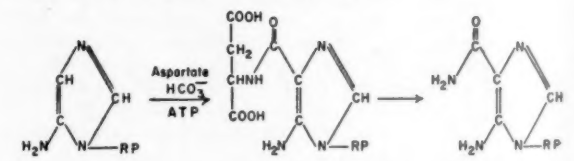


Fig. 5.

The product of these additions, aminoimidazole-carboxamide ribotide now adds a one-carbon fragment, a reaction again requiring the presence of a folic acid derivative. It is noteworthy that the initial inroad to this entire sequence was made when aminoimidazole-carboxamide was isolated (Stetten and Fox, 1945) and identified (Shive, Ackermann, Gordon, Getzendaner, and Eakin, 1947) as a product of micro-organisms whose folic acid production was inhibited by sulphonamide. The final step, closure of the six-membered pyrimidine

ring, yields hypoxanthine ribotide (HxRP) which is identical with inosinic acid (Fig. 6).

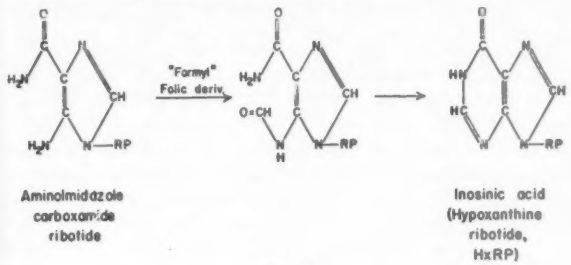


Fig. 6.

A summary of these several steps whereby the purine nucleus is assembled is given in Fig. 7. Here all irrelevant information is deleted and consideration is given only to the sequence of the successive additions of the atoms to form the condensed ring system of the purines.

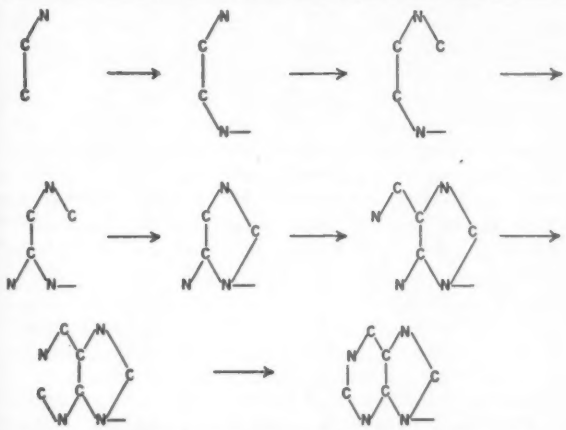
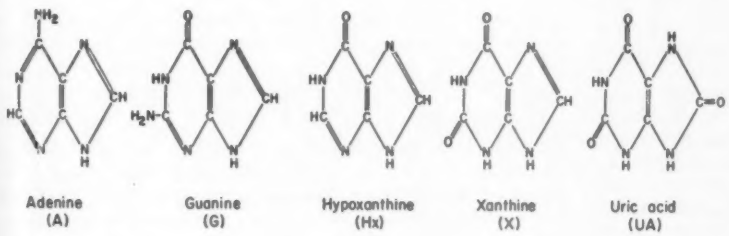


Fig. 7.—Sequence of introduction of atoms into purine nucleus.

Inosinic acid (HxRP) has several fates available to it. From the point of view of the defect in gout, perhaps the most interesting one is lysis to the free purine, hypoxanthine (Hx), followed by two oxidative steps, both catalysed by xanthine oxidase. The successive products are xanthine (X) and uric acid (UA), see Fig. 8.



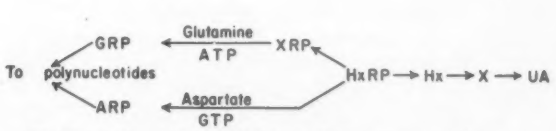


Fig. 8.— Interrelations of biologically important purines.

In man, the process has been pictured as stopping here, although the occurrence of further breakdown of uric acid, uricolysis, has been established as occurring to a minor degree in normal man (Wyngaarden and Stetten, 1953).

Inosinic acid also serves as a precursor to the other purine nucleotides which occur as such and as polynucleotides, nucleic acids, in the body. On the one hand, inosinic acid may be oxidized to xanthylic acid (XRP), which is animated by glutamine, in the presence of adenosine triphosphate (ATP) to yield guanylic acid (GRP). On the other hand, inosinic acid may be aminated directly by aspartate, in the presence of guanosine triphosphate (GTP) to yield adenylic acid (ARP). Thus the two purine nucleotide types which occur in ribose nucleic acids arise from a common precursor.

The biosynthesis of polynucleotides is currently believed to stem from the ribose pyrophosphate derivatives of these two purines and the analogous pyrimidine derivatives, by the action of a recently described polynucleotide phosphorylase (Grunberg-Manago, Ortiz, and Ochoa, 1955). *In vitro* studies suggest that the composition of the polynucleotide may be determined in part by the composition of the mixture of mononucleotides from which it is formed. If this proves to be the case, there is clearly an advantage to the organism in the regulation of the ratio of generation of adenine and guanine nucleotides. As will be seen from Fig. 8, an elegant regulatory mechanism seems to be built in to the reactions involved. To make *guanine* nucleotides from hypoxanthine, *adenosine* triphosphate is required (Abrams and Bentley, 1955). To make *adenine* nucleotides from the same precursor, *guanosine* triphosphate is required (Lieberman, 1956). Because of this curious cross-linkage of feedbacks, if, for any reason, production of GRP is limited, a limitation in ARP production would be anticipated to ensue, and *vice versa*. Likewise an overproduction of GRP might be expected to result in an increase in rate of generation of the ARP, and *vice versa*. Thus, at a chemical level there exists a novel kind of homeostasis wherein, not the abundance of a substance, but rather the ratio of abundances of a pair of products tends to remain constant.

REFERENCES

Abrams, R., and Bentley, M. (1955). *J. Amer. chem. Soc.*, 77, 4179.
Goldthwait, D. A. (1956). *Fed. Proc.*, **15**, 263.
——, Greenberg, G. R., and Peabody, R. A. (1955). *Biochim. biophys. acta*, **18**, 148.
Grunberg-Manago, M., Ortiz, P. J., and Ochoa, S. (1955). *Science*, **122**, 907.
Kornberg, A., Lieberman, I., and Simms, E. S. (1954). *J. Amer. chem. Soc.*, **76**, 2027.
Levenberg, B., and Melnick, I. (1956). *Fed. Proc.*, **15**, 117.
Lieberman, I. (1956). *J. Amer. chem. Soc.*, **78**, 215.
Lukens, L. N., and Buchanan, J. M. (1956). *Fed. Proc.*, **15**, 305.
Shive, W., Ackermann, W. W., Gordon, M., Getzendaner, M. E., and Eakin, R. E. (1947). *J. Amer. chem. Soc.*, **69**, 725.
Stetten, M. R., and Fox, C. L., Jr. (1945). *J. biol. Chem.*, **161**, 333.
Warren, L., and Flaks, J. G. (1956). *Fed. Proc.*, **15**, 379.
Wyngaarden, J. B., and Stetten, D., Jr. (1953). *J. biol. Chem.*, **203**, 9.

(2) Acute Gouty Arthritis. By CHARLEY J. SMYTH (*Denver, Colo*): My remarks will be directed first to agents useful in the treatment of acute attacks of gouty arthritis, and second, to the measures that are effective in the prevention of acute attacks.

Agents useful in the treatment of acute gout are colchicine, desacetylmethylcolchicine (Colcemide), phenylbutazone, and the steroid hormones. Oral colchicine is still the proven, dependable, safe, and almost uniformly effective agent and is generally accepted as the "standard" in the control of acute attacks. In most instances, it is still the drug of choice. Recently, intravenous colchicine has been reported on favourably. Single doses of from 0·25 to 6 mg. in 3 to 10 ml. normal saline have been found safe, rapid, and effective. The advantage of this route is the absence of gastro-intestinal toxicity, and it is especially suitable for post-operative attacks.

Desacetylmethylcolchicine, a new alkaloid derived from *Colchicum autumnale*, is reported to be as effective as colchicine and to be without toxic effects. If these early reports are confirmed, this drug will have distinct advantages over colchicine, but many more clinical studies need to be done.

Phenylbutazone has proved to be dramatically effective in acute gout. In fifty consecutive patients with 65 acute attacks of gout, its use resulted in prompt relief of joint pain, followed within 24 to 48 hours by control of other signs of inflammation. The following oral programme has been adopted:

(1) A single large initial dose of 400 to 800 mg.;
(2) Two doses of 200 mg. each at 2- to 4-hour intervals;
(3) 300 to 400 mg. in divided doses during the next 2 to 3 days until all signs of joint inflammation have disappeared.

In this study, no toxic results occurred. Just how great is the risk of this drug in acute gout remains an unsettled question.

Cortisone, hydrocortisone, and corticotropin have all been shown to control acute attacks. The results are not uniformly good and therefore their use is reserved to instances where the above agents prove ineffective.

For the prevention of acute attacks, treatment must be continued indefinitely, and success depends upon the patient's willingness to submit to uninterrupted life-time therapy. Measures of proved value include:

(1) Reduction of activity to avoid unusual trauma to joints;
(2) Avoidance of foods known to initiate acute gouty episodes;
(3) Avoidance of drugs known to trigger acute attacks, such as liver extract, mercurial diuretics, insulin, ergotamine, etc.;
(4) Probenecid (Benemid) as continuous therapy in amounts adequate to keep the serum urate at a normal value.

The following additional measures are also useful:

(1) Daily colchicine in low doses of 1 to 2 mg.;
(2) Long-term sodium salicylates in high doses (90 gr. daily);
(3) Abstinence from alcohol.

The place of phenylbutazone in long-term low-dose therapy (200 to 300 mg.), is not yet established as effective and safe.

(3) Prevention and Treatment of Chronic Gouty Arthritis, with special reference to Benemid. By ELMER C. BARTELS (*Boston, Mass.*): The prevention of chronic gouty arthritis encompasses a programme of treatment aimed at forestalling the recurring acute attacks of gout which usually lead to gouty arthritis. There is, of course, the occasional patient with recurring gout, who does not develop chronic gouty arthritis even after 20 or 30 years.

The treatment of chronic gouty arthritis has two aims:

(1) Prevention of recurring acute gouty arthritis;
(2) Reversal of the late manifestations of gout, *i.e.* absorption of tophi and relief of bone damage.

Improvement in renal changes resulting from urate deposits, secondary pyelonephritis, and nephrosclerosis is desirable. Improvement in renal function with treatment has been reported, and clinical experience with present-day methods indicates that in most patients with gout the above aims can be met, at least in part.

If properly treated, gout can be controlled (not cured) with rare exceptions. To be successful, the treatment of gout must be highly individualized, as is the therapy of diabetes, since there are wide gradations of this disease.

The method of treatment to be instituted depends on many factors, such as frequency of attacks, duration of attacks, the presence of tophaceous gout, and possibly the presence of hyperuricaemia (uricacidaemia) without gout or so-called familial gout. If a patient has a mild attack every 1 to 2 years which responds promptly to colchicine, he may choose to continue this programme. The presence of tophaceous gout necessitates energetic maintenance treatment to avoid further progress of the disease with resulting deposits of urates. The question whether asymptomatic hyperuricaemia is harmful has not as yet been resolved. If it is associated with renal stones, the patient needs treatment—diet, administration of Benemid, and alkalinization of the urine. The essentials of anti-gout maintenance therapy include:

(1) A low purine and low fat diet;
(2) No alcohol intake;
(3) The use of a uricosuric agent.

Effective uricosuric agents include Benemid, which is preferred at present since it is well tolerated (the incidence of sensitivity reactions is 1 to 2 per cent.); sodium salicylate in 90 gr. daily doses (highly uricosuric, and not well tolerated because of side-effects); Butazolidin (G-25671), a new derivative said to be low in toxicity; Tromexan which has uricosuric properties similar to those of Benemid in dosages far below those required for anticoagulation. It appears that all the uricosuric drugs are potentiated by alkalinization of the urine, this is especially true of salicylates.

The major goal of anti-gout therapy is a sustained normal level of serum uric acid. If this is accomplished over a prolonged period of time, the gout may be controlled. The dose of a uricosuric agent such as Benemid may vary from 250 to 3,000 mg. daily.

Gout is amenable to control by individualized maintenance therapy. The benefits of proper treatment are manifested by relief of attacks, the return of the serum uric acid level to normal, reduction in the size of existing tophi, healing of draining tophi, and reversal of bone changes.

Discussion.—MODERATOR GUTMAN: A good many queries that came to us dealt with the matter of diet. This has been touched upon already, but I think it might be helpful to review the situation, to crystallize the thinking of the panel. Dr. Stetten, would you present the case for diet from the metabolic point of view?

DR. STETTEN: Two aspects of this disease are seemingly only remotely related: the colchicine-responsive recurrent arthritis and arthralgia, on the one hand, and the increase in quantity of urate in the body, reflected by ultimate deposit of tophi, on the other.

At present I believe none of us has a clear idea how these two phases of the disease may be related, and there are some, perhaps, who suspect that this relationship may be very remote.

As far as I am aware, diet comes into consideration only in regard to the second of these two defects. The best reference that we have devised so far, to consider the possible effects of diet, relates to a mathematical quantity that we have termed the miscible pool of uric acid.

This may be simply defined as that quantity of uric acid in the body of a man capable of mixing promptly with injected uric acid. It is a concept analogous to the more familiar body space concept of the physiologist. This pool of uric acid, which is of the order of 1 g. uric acid in normal man, expands enormously in gout. It has been observed to expand in every gouty subject, so far as I am aware, who has been studied by this method. It has sometimes been observed to expand in the face of an apparently normal serum uric acid concentration.

The effects of diet anticipated are that, if the purine content of the diet is kept low, this contribution to the miscible pool at least can be eliminated. It is quite easy to secure a diet which is virtually devoid of purine. Most vegetables are practically devoid of them, eggs are very low, and milk is poor in them.

Some years ago our group collaborated with Dr. Gutman's group in a study of the effect of the protein content of the diet upon the amount of the miscible pool of uric acid. We concluded that the quantity of urate produced from dietary amino acid was enhanced when the protein content of the diet was increased.

On the basis of these findings, to reduce the miscible pool of uric acid, one would keep the protein content of the diet within reasonable bounds.

DR. BARTELS: We advise our patients to keep their diet low in purine and fat, and to avoid the use of alcohol.

Some patients who have very mild gout, on that plan alone, might be able to avoid trouble, but we have had patients who were under control on Benemid, with normal uric acid levels, who used alcohol to excess and followed no diet restrictions whatever and still maintained control. I do not suggest that as a means of treatment, but some patients neglect what we tell them, yet we are still bound to try to treat them.

MODERATOR GUTMAN: You see, there is still a good deal of difference of opinion in regard to the place of dietary regulation in the management of gout, although perhaps not as much as one might expect. Our own point of view in respect to diet is to distinguish the objectives of restriction, whether for prevention of the recurrence of acute gouty arthritis, or whether for retarding the development of chronic gouty arthritis.

I think there is every reason to believe, from metabolic considerations, that the more purine and protein and fat are consumed, the more uric acid is formed and retained in the body. Although we cannot measure this on a day-to-day basis, it is reasonable to believe that excesses in these food components will accelerate the rate of tophaceous deposit.

In respect to acute gouty arthritis, my experience is like that of the others. We find that there are important differences among patients, which cannot be predicted from any clinical or laboratory study, except by careful history taking, and we adjust dietary restriction to the individual requirements of the particular patient. Some gouty subjects can eat and drink almost anything they wish, without any apparent detriment, and we allow them a reasonably free choice in diet. In those in whom restriction seems important, as judged by their own experience, we attempt to restrict the diet and alcohol intake.

Dietary regulation for prevention of the recurrence of acute attacks is, then, empirical, the underlying mechanism not being clear.

This question bears on the prophylactic use of colchicine; it is so important in the practical management of gout that I hope you will permit me to review our own experience in this regard, as recently compiled by Dr. Yü.

We have given 112 gouty subjects with a prior history of multiple acute attacks a prophylactic colchicine regimen in doses varying from 0·5 to 1·5 mg. daily by mouth, the dosage being adjusted to individual requirements by trial and error.

Of these 112 gouty patients, 31 received daily prophylactic colchicine for from 5 to 10 years; 44 for 3 to 5 years; 28 for 1½ to 3 years, and nine for 1 to 1½ years. These are long-term statistics, because a judgment based on short-term observations cannot be of much value, in view of the unpredictability of the acute attacks.

Evaluation in thirteen of our 112 patients was difficult because of the irregularity of previous attacks; of the remaining 99, 67 were virtually symptom-free during the period of observation.

In thirty cases, attacks were satisfactorily reduced in number and severity, but control was less complete. Prophylaxis in the two remaining cases was unsatisfactory. No significant toxicity or intolerance was noted in this series.

We have been interested, also, in the question of the usefulness of Benemid as a prophylactic in acute gouty arthritis. Of the 67 patients showing excellent results, 28 were tophaceous and received Benemid regularly, and 21 had little or no tophaceous deposit and received colchicine only. We found no significant difference in the recurrence of acute attacks between the patients who received Benemid plus colchicine, and those who received colchicine alone.

In 27 patients who took colchicine and Benemid regularly but then discontinued Benemid, no definite effect was observed on the recurrence of acute gouty arthritis. On the other hand, nine patients who discontinued colchicine had a recurrence of acute gouty arthritis sooner or later.

Colchicine is valuable in preventing the recurrence of acute gouty arthritis. It may not prevent recurrences altogether, but it reduces the incidence and severity of the attacks, if the dosage is sufficient and the diet appropriately regulated.

Combining Benemid with colchicine is, I think, advantageous in patients with extensive chronic gouty arthritis

but I doubt whether the administration of Benemid alone to patients without chronic involvement is of much value in preventing the recurrence of acute gouty arthritis.

DR. BARTELS: This list of patients is, perhaps, the longest and most carefully controlled of any group with which I am familiar, in which daily oral colchicine has been used as a prophylaxis. I think any additional studies would be welcome.

MODERATOR GUTMAN: A question directed to Dr. Smyth:

There has been a good deal of discussion and confusion about the use of phenylbutazone as a uricosuric agent. Is it or is it not uricosuric, and should it be used as a uricosuric agent?

DR. SMYTH: If you give enough phenylbutazone to raise the blood level to somewhere between 10 and 11 mg. per cent., the drug is usually uricosuric.

We wondered whether it had any promise as a chronic urate diuretic, or any prophylactic value. As an experimental study we have now followed seven patients for from 59 to 313 days of continuous therapy with 300 to 400 mg./day. None had an acute attack of gout, but there was no consistent lowering of the serum urate. Since we have much safer uricosuric drugs, Benemid and sodium salicylate, there is no reason to run the risk of long-term phenylbutazone therapy. I would not recommend it as a therapeutic measure for chronic gouty arthritis.

MODERATOR GUTMAN: This next question concerns the management of the gouty subject who has chronic gouty arthritis but also has some indication of renal damage.

Dr. Bartels, is the presence of renal damage a contraindication to the use of uricosuric agents? I wish you would also comment, as you did in your prepared discussion, on the precise management of a case in which there is a history of renal colic due to the formation of calculi.

DR. BARTELS: It is recognized that a fair percentage of older patients, particularly those with tophaceous gout, do have evidence of renal disease. It was initially felt that Benemid should not be given to patients with a high degree of nitrogen retention. On the other hand, this is the type of patient who needs particular help, and, if it is possible to reverse his renal disease, we can be of great help to him.

We have had several patients with high degrees of nitrogen retention who developed anaemia, and tolerated Benemid very well. It is very difficult to produce much uricosuric effect or to lower the serum uric acid substantially. There is certainly no objection to the use of Benemid, and they tolerate it perfectly.

As regards renal calculi, I see no reason why their presence should preclude the use of Benemid, nor have I seen a higher incidence of stone formation in patients who are given Benemid.

It is true that in patients with a history of renal calculi it seems advisable to alkalinize the urine, but we do not do this as a routine measure.

MODERATOR GUTMAN: There are some questions about secondary gout, of which you have heard a good deal in recent years. There is an increased incidence of gout in association with certain haematopoietic disorders, notably myeloid metaplasia, primary polycythaemia, and rarely also the leukaemias and haemolytic anaemias.

The management of secondary gout which presents as both acute and chronic gouty arthritis with extensive tophi, is always a difficult matter, but the general principles of therapy applicable in primary gout may be followed. The acute attacks respond to colchicine, ACTH, and phenylbutazone, and we use uricosuric agents such as Benemid in the prevention and treatment of tophaceous deposits.

In such cases, treatment is always difficult because of the underlying disease. Sometimes treatment of the underlying leukaemia or polycythaemia may precipitate acute gouty attacks which are very difficult to avoid in such circumstances.

Another questioner asks: What is the current status of the newer uricosuric agents compared with probenecid?

This refers to certain derivatives of phenylbutazone such as G-25671, which have marked uricosuric potency. I agree with Dr. Bartels and Dr. Smyth that these drugs are still very much in the experimental stage. We now have preparations that are powerful uricosuric agents and have also some mild anti-inflammatory activity, but they require more extensive experimental work before they can be made available for general use.

* * *

PANEL DISCUSSION

Teaching Collection of Lantern Slides on the Pathology of Arthritis and Rheumatism

Introduction: CURRIER MCEWEN, *New York, N.Y.*

Subcommittee on Pathology of the Arthritis and Rheumatism Foundation:

LENT C. JOHNSON, *Washington, D.C.*
J. PETER KULKA, *Boston, Mass.*
LEON SOKOLOFF, *Bethesda, Md.*
ROGER TERRY, *Washington, D.C.*

Discussion: D. MURRAY ANGEVINE, *Madison, Wis.*
C. HOWARD HATCHER, *Chicago, Ill.*

* * *

PAPERS PRESENTED BY TITLE ONLY:

New Plan of Treatment of Low Back Pain. By JOSEPH E. ALLEGRETTI, *Chicago, Ill.*

Comparison of the Results of the Intra-Articular Use of Prednisolone Acetate with Hydrocortisone Acetate. By ARTHUR W. BAGNALL, *Vancouver, B.C., Canada.*

Occurrence of Multiple Fractures and Other Connective Tissue Alterations in Suckling Rats injected with Beta-Aminopropionitrile (Lathyrus Factor). By JACKSON J. CLEMMONS and D. MURRAY ANGEVINE, *Madison, Wisconsin.*

Rheumatoid Synovial Cyst of the Hip: Report of Three Cases. MARK B. COVENTRY, ALLEN D. WEINER, and HOWARD F. POLLEY, *Rochester, Minn.*

Results of a Simplified Sheep Cell Hemagglutination Test, using Mineral Acid for Precipitation of the Serum Euglobulin Fraction. H. WILLIAM CRAIG, GRACE P. KERBY, and ELBERT L. PERSONS, *Durham, N.C.*

Effect of Hydrocortisone and Growth Hormone on S^{35} Fixation in the Stomach of Hypophysectomized Rats. By CHARLES W. DENKO, *Chicago, Ill.*

Methods for the Clinical Appraisal of a New Therapeutic Agent in Rheumatoid Arthritis. By JACK R. DORDICK, *New York, N.Y.*

L.E. Phenomenon in Rheumatoid Arthritis. By IRVING A. FRIEDMAN, JEROME F. SICKLEY, ROBERT M. FOSKE, ARNOLD BLACK, PAUL S. REEDER, DAVID BRONSKY, and CHARLOTTE FELDHAKE, *Chicago, Ill.*

Occurrence of Rheumatoid Arthritis in Twins. By ARTHUR J. GROSSMAN, PAUL LEIFER, and ROBERT C. BATTERMAN, *New York, N.Y.*

Disability Evaluation in Degenerative Arthritis. By WM. N. HARSHA, *Oklahoma City, Okla.*

Coincidence of the "Fibrositis Syndrome" with Degenerative Joint Disease in Peripheral Joints: A Survey of 300 Consecutive Admissions to an Arthritis Clinic. By JED H. IRVINE, *New York, N.Y.*

Role of Specific Rheumatological Skills and Other Disciplines in the Development of Musculoskeletal Nosology. JED H. IRVINE, *New York, N.Y.*

Objective Evaluation of Patients with Rheumatic Diseases. By W. K. ISHMAEL, R. W. PAYNE, J. N. OWENS, JR., A. A. HELLBAUM, and MARY L. DUFFY, *Oklahoma City, Okla.*

Administration of Phenylbutazone for 12 to 54 Months in 100 Cases of Rheumatoid Arthritis and Ankylosing Spondylitis. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, W. EDWARD NAUGLER, and BARBARA CHAMPLIN, *San Francisco, Calif.*

Coincidence of Other Disorders in 520 Gouty Patients. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, W. EDWARD NAUGLER, and BARBARA CHAMPLIN, *San Francisco, Calif.*

Paper Electrophoresis Study of Serum Protein in Rheumatoid Arthritis. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, W. E. NAUGLER, and EMMET L. DURRUM, *San Francisco, Calif.*

Use of Cortisone and Renal Arteritis in Scleroderma. By IRVING LEINWAND, A. WILBUR DURYEE, and MAURICE N. RICHTER, *New York, N.Y.*

Comparison of a Colorimetric and an Enzymatic Method for Determining Serum Uric Acid. By ELDON A. MANKLE, ESTHER LARSON, and WILLIAM C. KUZELL, *San Franciscio, Calif.*

Amyloidosis in Rheumatoid Arthritis: A Clinico-Pathological Study. By STANLEY MARCUS, LEO KAPLAN, ROBERT SWEZEY, HOWARD WEINBERGER, and MELVIN LEVIN, *Los Angeles, Calif.*

Effect of Prednisone and Prednisolone in Rheumatoid Arthritis: One Year Follow-up Study. By DAVID H. NEUSTADT and ROBERT MCCLENDON, *Louisville, Ky.*

Local Effects of Hydrocortisone by Needle or Hypospray and Ultra-sound. By MAX K. NEWMAN, *Detroit, Mich.*

Relation of Calcified Tendonitis to Cardiovascular Disease. By JOSEPH NEY, *Washington, D.C.*

Observations on Gradations of the Hargraves Cell Phenomenon in Rheumatoid Arthritis. By J. N. OWENS, JR., D. BERRY, R. W. PAYNE, M. L. DUFFY and W. K. ISHMAEL, *Oklahoma City, Okla.*

Increased Capillary Fragility in Rheumatoid Arthritics. By CHARLES M. PLOTZ and RUBIN KLEIN, *Brooklyn, N.Y.*

Importance and Recognition of Acute Abdominal Episodes in Systemic Lupus Erythematosus. By VICTOR E. POLLAK, ROBERT M. KARK, PETER PULOS, and IRVING E. STECK, *Chicago, Ill.*

Systemic Lupus Erythematosus and Pregnancy. By VICTOR E. POLLAK, ROBERT M. KARK, IRVING E. STECK and PETER PULOS, *Chicago, Ill.*

Relationship of Renal Structural Changes to Renal Function in Lupus Nephritis. By VICTOR E. POLLAK, ROBERT M. KARK, CONRAD L. PIRANI, ROBERT C. MUEHRCKE, and IRVING E. STECK, *Chicago, Ill.*

Chloroquine Therapy in Rheumatoid Arthritis. By ROBERT E. RINEHART, *Wheeler, Oregon.*

Peculiar Familial Form of Primary Systemic Amyloidosis. By LAWRENCE E. SHULMAN and FREDERICK C. BARTTER, *Baltimore and Bethesda, Md.*

Chrysotherapy: I. Urine Excretion Rate of Gold as a Guide to Treatment. By RICHARD T. SMITH, WILLIAM P. PEAK, KENNETH M. KRON, and IRVIN F. HERMANN, *Philadelphia, Pa.*

Unrecognized Gouty Arthritis diagnosed by Synovial Biopsy. By LEON SOKOLOFF, ROGER L. BLACK, RUTH H. WICHELHAUSEN and JOSEPH J. BUNIM, *Bethesda, Md,* and *Washington, D.C.*

Observations on Long-Term Administration of Phenylbutazone in Musculoskeletal Disorders. By OTTO STEINBROCKER, *New York, N.Y.*

"Anecdotal" Appraisal of a Clinical Experience with 150 Patients with Rheumatoid Arthritis treated with Prednisone. By BERTRAND L. STOLZER, JAMES H. BARR, JR., CARL H. EISENBEIS, JR., RICHARD WECHSLER and H. M. MARGOLIS, *Pittsburgh, Pa.*

Are Salicylate Benefits mediated by Steroids? CHESTER B. THRIFT and EUGENE F. TRAUT, *Chicago, Ill.*

Aortitis of the Root of the Aorta with Aortic Valvular Insufficiency in Rheumatoid Arthritis. By JONAS VASSITIS, CLIFFORD G. PILZ, and MAX M. MONTGOMERY, *Chicago, Ill.*

Anti-Rh Antibody for demonstrating the Agglutination Activating Factor. By JOHN H. VAUGHAN and MARION V. WALLER, *Richmond, Va.*

Oral Colcemide in the Treatment of Acute Gout. By STANLEY L. WALLACE, JACOB COLSKY, and MORRIS BANOWITCH, *Brooklyn, N.Y.*

Comparison of the Metabolism of Hydrocortisone in the Normal and Rheumatoid Synovial Cavity. By HILDEGARD WILSON, RICHARD FAIRBANKS, CURRIER MCEWEN, and MORRIS ZIFF, *New York, N.Y.*

Efficacy of Colchicine Prophylaxis for Recurrent Acute Gouty Arthritis. By T. F. YÜ and ALEXANDER B. GUTMAN, *New York, N.Y.*

Results of the Sensitized Sheep Cell Agglutination Test in Chronic Arthritic Diseases. MORRIS ZIFF, GEORGES FALLET, JOSEPH LOSPALLUTO, and CURRIER MCEWEN, *New York, N.Y.*

Use of Hydrocortisone in the Treatment of the Painful Shoulder (Film). By A. W. BAGNALL, *Vancouver, B.C.Canada.*

HEBERDEN SOCIETY

At a Clinical Meeting held on October 19, 1956, at the Wellcome Foundation, the following papers were read:

DR. OSWALD SAVAGE (*West London Hospital*): **A Study of the Course of Rheumatoid Arthritis during Continuous ACTH Administration with Clinical and Biochemical Observations.** Preliminary findings were reported from a study of cases of active rheumatoid arthritis treated with ACTH in which the clinical assessment had been correlated with the erythrocyte sedimentation rate (Westergren) and the level of 17-hydroxycorticosteroid output in the urine measured by Norymberski's method. These estimations were carried out by the Biochemical Department, West London Hospital, with the aid of a grant from the Empire Rheumatism Council.

The principal clinical measurements had been the total tenderness to firm pressure as measured in three grades and divided by the number of joints involved, and the grip measured by a Baumanometer cuff rolled and placed in a specially designed cover. Control groups had been studied in patients under treatment with rest, with salicylates, and with gold. In these there had been no variation from the normal levels of 17-hydroxycorticosteroid excretion in the urine. A difference in the strength of different batches of ACTH used had been apparent and it has been found most practical to keep patients on the same batch.

The patients were admitted to hospital in the first instance and a base-line of daily 17-hydroxycorticosteroid excretion was obtained before treatment was started. While in hospital they were taught to inject themselves with ACTH subcutaneously and this had been found a practical procedure. Some patients had injected themselves daily for as long as 3 years without difficulty and without local inflammation.

The patients in this study had been given sufficient ACTH to suppress symptoms and the erythrocyte sedimentation rate and the level of 17-hydroxycorticosteroid output in urine had been measured regularly.

The clinical response of patients in this group had been satisfactory, but the pattern of response had varied.

Clinical improvement had been accompanied in some cases by a wide variation in the level of 17-hydroxycorticosteroid output in the urine; in others suppression of symptoms had been maintained only when the adrenal cortex was continuously stimulated; in a third group it had been found possible to withdraw ACTH without clinical relapse after adrenal stimulation with a good clinical response and a fall in the erythrocyte sedimentation rate.

This work was carried out with the aid of the Dan Mason Foundation, West London Hospital Medical School.

DR. A. J. POPERT (*West London Hospital*): **Effects of Stress in Patients with Rheumatoid Arthritis during Adrenal Stimulation.** Normal people, when subjected to stress, consistently showed an increased urinary excretion of 17 OHCS: two patients who underwent oöphorectomy showed a typical crescendo rise with peak levels two or three times higher than normal on the day after operation.

By contrast, patients with rheumatoid arthritis who were under treatment with ACTH did not regularly show an increased excretion during periods of stress. For example, a man who had an antrostomy while receiving 30 units ACTH daily showed a sharp fall in excretion over the operative period, and a woman who suffered from a severe orbital infection while receiving 30 units ACTH daily showed a lower level of excretion during the whole period from onset to operation and recovery. A man receiving 40 units ACTH daily showed a steep increase in excretion on the first day of a series of gastro-intestinal haemorrhages; this was followed by a progressive fall as his condition deteriorated, and culminated in a very large increase in excretion during the days when death was approaching.

These results suggest that, while the production of adrenocortical hormones in response to stress may some-

times be limited by concurrent administration of ACTH, the factor of varying tissue utilization may influence the amount of 17 OHCS excreted in the urine.

DR. P. S. DAVIS (*West London Hospital*): **Relationship between the Clinical and Biochemical Findings in Rheumatoid Arthritis during Steroid Therapy.** In this study, treatment was based primarily on the clinical assessment and no attempt was made to maintain continuous adrenal stimulation as measured by 17-hydroxycorticosteroid excretion. Comparing the clinical and biochemical responses in these patients, it was found that whenever the corticosteroid excretion indicated definite adrenal stimulation there was some clinical response, but that there was no close correlation between the clinical course and level of corticosteroid excretion.

The majority of patients who received a constant dose of ACTH showed an initial rise in corticosteroid excretion, but after a period this fell to the normal range and did not rise again unless the dose was altered. Some patients relapsed clinically when corticosteroid excretion fell, as would be expected, but others maintained their clinical improvement.

Temporary decreases in corticosteroid excretion were also observed in association with exacerbations of arthritis or some form of stress.

Comparison of the proportion of an oral dose of hydrocortisone that can be estimated in the urine by various chemical methods and by radio-active studies, indicates that a considerable fraction is, in normal subjects, excreted in the form of compounds which are outside the range of 17-hydroxycorticosteroid estimations. Regular estimations of corticosteroid excretion were therefore performed on a small group of patients receiving long-term treatment with cortisone or hydrocortisone. It was found that there was a tendency for corticosteroid excretion to decrease in association with the minor exacerbations of arthritis that some of these patients experienced (no more severe forms of stress occurred in this group).

It is most probable that the fall in corticosteroid excretion after the initial rise is due to the development of a degree of resistance to ACTH, so that when clinical improvement is maintained there may have been a natural decrease in activity of the disease. It is possible, on the other hand, that the temporary decrease seen in association with exacerbations of arthritis or with stress may be due to increased metabolism of hydrocortisone into compounds outside the range of 17-hydroxycorticosteroid estimations during a phase of activity of the arthritis.

These apparent anomalies did not detract from the practical value of regular corticosteroid assays, which are considered to be essential for the satisfactory control of ACTH therapy. It is suggested, however, that treatment should be based primarily on the clinical course of the disease.

DRS. F. T. G. PRUNTY, R. V. BROOKS, and B. E. CLAYTON (*St. Thomas's Hospital, London*): **Factors influencing the Response of the Human Adrenal Cortex to Corticotrophin.** With the advent of partially purified preparations of corticotrophin it was hoped that the confusion which had arisen with earlier, less purified materials would be reduced. A potent cause of uncertainty in assessing these properties with respect to the human adrenal cortex was their apparent proneness to destruction in the tissues before reaching the target organ (Prunty, 1956). The newer materials studied have included Armour "H.P." gels, Wilson gel, and Crookes zinc-protamine corticotrophin. From the start it was found, as with older preparations, that large variations occurred between patients and batches of corticotrophin when 17-ketosteroids were measured. For example, ketosteroids varying between 13 and 62 were obtained with dosages of 20 units 12-hourly of Batch 5, in different individuals. In two patients a reasonable relation between log dose and ketosteroids could be obtained although the curves were widely separated.

It was known that changes in ketosteroids were not the most sensitive indicators of increasing adrenal cortical activity, but with the advent of the better measurement of ketogenic steroids (Norymberski, Stubbs, and West, 1953) the situation remained similar. In ten individuals with presumed normal adrenals, including five rheumatoid patients, the maximum levels in the 4-day response regime (Prunty, 1956), using 20 units 12 hourly of Batch 5 were $61 \pm 6{\cdot}3$ (S.E.) mg. daily ketogenic steroids and $28 \pm 3{\cdot}8$ (S.E.) mg. daily ketosteroids. This still shows a wide variation of response. From these figures, and on the basis of a 40 per cent. recovery of administered cortisone as ketogenic steroids, the cortisone equivalent of this dose of corticotrophin is approximately 150 mg. daily. From a long-term study of three patients with hypopituitarism (Prunty, 1956), it was estimated that 20 units 24-hourly produced normal ketogenic steroid excretion of about 15 mg. daily; this would correspond to the administration of 37·5 mg. cortisone daily. The effect of administering the larger dose in two portions 12-hourly was greater than the predicted effect of its administration *in toto* at 24-hourly intervals.

The response of the adrenal immediately ceases when the administration of corticotrophin ceases. This occurs at once when intravenous administration is discontinued, and in 24 to 48 hours after the last intramuscular injection. Whilst the 4-day administration of corticotrophin (20 units 12-hourly) seems valuable for test purposes, it is often too short a period to produce a maximal response. For example, one patient took 12 days to reach a maximum of 71 mg. ketogenic steroids, and another reached 81 mg. after 28 days. On the other hand, considerable variation may occur in day-to-day excretion levels when the plateau has been reached. During three consecutive days variations were found between 57 and 71 mg. ketogenic steroids, and in another instance between 33 and 63 mg. In a third patient, values of 44 and 26 mg. were found on consecutive days.

In attempting to correlate the response of patients with different batches of corticotrophin, we have assayed by the Sayers' test, employing intravenous injection, in all fifteen batches of corticotrophin of various manu-

facture. The results obtained varied between 0·3 and 7 times the labelled potency, the fiducial limits of the assays being less than 50 to 400. These assays included the later gel batches. Three other gel batches gave low potencies and it was not possible to obtain good regression in the assays (10, 12, 13). Batch 10 appeared to be considerably less than half the expected potency. In the case of Batch 12 the potency was approximately that expected, but on assay 3 months later no response could be obtained. Batch 10 was clinically very feeble. On changing from 20 units 12-hourly of Batch 5, which assayed at 1·2 times the labelled potency, to the same dose of Batch 10, the ketogenic steroids promptly fell from 47 to 10 mg. daily in a patient with rheumatoid arthritis. Batch 10 was given to four other patients, three of whom gave no response (one of these was receiving it intravenously), while the fourth gave a feeble response by the intravenous route. Batch 13 had a significantly poorer effect in five human individuals than Batch 5. On the other hand, a patient with Cushing's syndrome with highly sensitive hyperplastic adrenals gave the expected intense response to Batch 13. Batch 12 evoked reasonable responses in three patients.

Observations in one patient with rheumatoid arthritis suggested the possibility of decreased adrenal responsiveness to corticotrophin. After 108 days' treatment with three batches (5, 13, 14) of corticotrophin, in doses down to 10 units 12-hourly, the response to 20 units 12-hourly of Batch 5 appeared significantly less than at the commencement of therapy. The falling ketosteroid response observed paralleled the clinical state of the patient's condition. This is probably an example of the developing refractoriness encountered by West (1956).

Factors which are involved in the response of patients to corticotrophin include, therefore, the potency of the hormone employed, variation in responsiveness of adrenals of patient, duration of dosage, marked sensitivity to change of dosage levels in a given individual, and decreasing sensitivity of the adrenals with passage of time. In addition to these, various other factors depending upon the endocrinological status of the individual modify the response (see Prunty, 1956). With these possible variations in behaviour, it will be apparent that the production of the required response to injections of a given dose of corticotrophin is a difficult matter. Satisfactory therapeutic control requires precise and detailed information concerning the response of each individual.

REFERENCES

Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, **1**, 1276.
Prunty, F. T. G. (1956). *Brit. med. J.*, **2**, 615, 673.
West, H. F. (1956). *Annals of the Rheumatic Diseases*, **15**, 124.

ARTHRITIS AND RHEUMATISM FOUNDATION

Eastern Pennsylvania Chapter

On October 31, 1956, the first teaching sets of pathology slides in the field of arthritis and the rheumatic diseases were presented on behalf of the Foundation by Dr. Leon Sokoloff, Senior Surgeon of the U.S. Public Health Service, and Research Pathologist of the National Institute of Arthritis and Metabolic Diseases, to the Graduate School of the University of Pennsylvania, the Hahnemann Medical College, the Jefferson Medical College, Temple University, the University of Pennsylvania, and the Women's Medical College of Pennsylvania. With each set of a hundred slides was a teaching syllabus, including a description of the joint damage in each specimen and a clinical account of the patient from which it was obtained.

The preparation and collection of the slides, which was sponsored by the Medical and Scientific Committee of the Arthritis and Rheumatism Foundation,* was greatly facilitated by the co-operation of the Armed Forces Institute of Pathology. Sets are also being distributed to the 45 Chapters of the Arthritis and Rheumatism Foundation and will be available for loan to medical groups in each area.

Dr. Philip R. Trommer, President of the Eastern Pennsylvania Chapter, said that professional education in this field of medicine had been hampered by a lack of available specimen material; he hoped that the slides would also prove effective in stimulating further research in arthritis and the rheumatic diseases.

The presentation was followed by the Sixth Annual Ralph Pemberton Memorial Lecture, sponsored jointly by the Philadelphia Rheumatism Society and the Eastern Pennsylvania Chapter of the Arthritis and Rheumatism Foundation. Dr. Leon Sokoloff spoke on "The Pathology of Arthritis and Rheumatism".

* See p. 408.

Ann. rheum. Dis. (1956), **15**, 413.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Relationship of Sydenham's Chorea to Infection with Group A Streptococci. TARANTA, A., and STOLLERMAN, G. H. (1956). *Amer. J. Med.*, **20**, 170. 3 figs, 11 refs.

The relationship between Sydenham's chorea and streptococcal infections was studied by analysing the case histories of patients observed during a first attack of chorea under conditions in which streptococcal infection could be controlled and the serum antibody titre determined.

Of ten patients with "pure" chorea who were seen within 5 months of the onset of choreiform activity, eight had a serum antistreptolysin-O (ASO) titre of more than 200 units per ml.; of the two remaining patients, one had a serum antihyaluronidase titre of 300 units per ml., while the serum of the other showed no increase in the titre of the three streptococcal antibodies studied. In another series 27 out of 41 patients had serum ASO titres of more than 200 units per ml. It appeared that the earlier the patient was tested after the onset of chorea, the higher was the serum ASO titre, although, in general, the titre in these cases was rather lower than that observed in acute rheumatic fever. In those cases in which chorea is associated with other manifestations of acute rheumatism it tends to follow them after an interval as long as 7 months, with no evidence of a fresh streptococcal infection during that time, and by the time chorea develops the serum content of antistreptococcal antibodies may have fallen to normal.

The authors consider it reasonable to assume that the same relatively long latent period intervenes between the streptococcal infection and the onset of chorea when it occurs as an isolated phenomenon, and suggest that this may explain the lack of immunological evidence of streptococcal infection in some cases of "pure" chorea.

G. Loewi.

Pattern of Respiration in Rheumatic Heart Disease. SHEPHARD, R. J., and VENNER, A. (1956). *Brit. Heart J.*, **18**, 241. 1 fig., 26 refs.

The pattern of respiration was examined at Guy's Hospital, London, in 116 patients with rheumatic valvular heart disease—55 with pure mitral stenosis and the remaining 61 with other valvular lesions—measurements being made both at rest and after standard pedalling exercise of the respiratory minute volume, respiratory rate, tidal volume, expiratory reserve, and pulmonary arterial and capillary pressures. The resting vital capacity and expiratory reserve were considerably reduced in both groups. The increase in respiratory rate with exercise was almost double that of normal subjects, and this gives a useful indication of the degree of pulmonary congestion; at the same time, however, respiration became mechanically less efficient. The symptom of dyspnoea seemed to be associated primarily with the reduction in vital capacity, although there was no clear correlation between the latter and the degree of disability or the pulmonary vascular pressures.

The conclusion is reached that in the assessment by laboratory methods of the symptom of dyspnoea, account should be taken both of the reduction of vital capacity and of the loss of respiratory efficiency.

A. Schott.

Pathogenesis of Valvular Thickening in Rheumatic Heart Disease. TWEEDY, P. S. (1956). *Brit. Heart J.*, **18**, 173. 12 figs, 27 refs.

In a study of the pathogenesis of valvular thickening in rheumatic heart disease, the cardiac valves of 29 patients dying from this condition were examined at the Royal Victoria Infirmary, Newcastle upon Tyne. Examination for surface deposits showed that these occurred most often in the commissures between thickened cusps on the contact line of the valve and on the extreme tip; they were less commonly found on the chordae tendineae and elsewhere. Vegetations were shown to consist of acidophil material which stained partly for fibrin and partly not. A study of the changes immediately preceeding the formation of vegetation revealed that neither fibrinoid change nor underlying inflammation was necessarily present at the onset of thrombus deposition, though some damage to the endothelium appeared to be a necessary pre-condition.

Thrombus deposits were found on valves at all stages of the disease, and these are considered to be responsible for much of the thickening in rheumatic valvular disease.

They also appeared to be the cause of the fusion of chordae to each other and to valve cusps, as well as of the incorporation of chordae tendineae into valve cusps. The thrombus deposits were found to consist of fibrin and probably also platelets. Since they were very widespread it is suggested that most of the actively proliferating tissue in the valves in acute valvulitis may be due to the organization of successive thin deposits rather than to a primary proliferation. *R. B. Lucas.*

Rheumatic Fever Pneumonitis: A Clinical and Pathologic Study of 35 Cases. LUSTOK, M. J., and KUZMA, J. F. (1956). *Ann. intern. Med.*, **44**, 337. 13 figs, 14 refs.

Pneumonitis was found at necropsy in 35 cases of rheumatic fever terminating fatally and rapidly in the acute phase. It was found that the pneumonitis was not a specific entity, being similar to that found in a number of other diseases. However, the frequency of the condition, which was not diagnosed before death in any of these cases, and the magnitude of the pathological changes, are considered to warrant the designation of "rheumatic fever pneumonitis". In all cases rheumatic carditis was present, but the degree and prominence of respiratory distress, cough, chest pain, cyanosis, and haemoptysis were out of proportion to the general condition of the patient and the degree of cardiac involvement. One patient, in whom the condition was suspected ante-mortem, was treated with ACTH, with regression of fever, erythrocyte sedimentation rate, and carditis, but the respiratory distress increased to the fatal termination. Death occurred in fifteen cases within 2 weeks of the onset of pneumonitis. [The incidence of the condition and the total number of cases of rheumatic fever from which this series is derived are not specified.]

There were no significant laboratory findings. Radiographs of the chest showed increased perivascular markings arising from the hilus and progressing to nodulation, confluence, and massive consolidation with relatively clear apices and bases. The main morbid anatomical findings were:

(1) alveolar haemorrhages;
(2) alveolar-wall necrosis;
(3) hyaline membranes;
(4) proliferation of alveolar lining cells;
(5) Masson organized bodies;
(6) bronchiolar changes;
(7) changes in the blood vessels.

These findings are fully and well illustrated and a number of radiographs are reproduced. A useful bibliography is given. *Harry Coke.*

Diagnostic Significance of Plasma Protein Changes in Acute Rheumatic Fever. JACOX, R. F. (1956). *N.Y. St. J. Med.*, **56**, 672. 7 figs, 10 refs.

Quantitative estimation of the inflammatory process is of great importance in rheumatic fever. One of the most widely used methods of assessment is determination of the erythrocyte sedimentation rate (E.S.R.); another, more recent, method is estimation of C-reactive protein in the serum. Both these methods depend on changes taking place in the serum protein components, and in rheumatic fever electrophoretic studies have shown that changes of a quantitative nature do occur. The discovery of the cationic detergent technique has made it possible to make frequent and consecutive determinations of serum protein fractions and to measure accurately the alpha and beta-gamma fractions as well as the albumin and fibrinogen concentrations.

During the past three years, the author, at the University of Rochester School of Medicine and Dentistry, New York, has studied some sixty patients with rheumatic fever, and the present paper concerns six of these whose serum was examined over a period of time by means of the cationic detergent fractionation technique. It is pointed out that in healthy subjects the plasma protein pattern is remarkably constant. Thus in a healthy man of 26 in whom serum proteins were analysed weekly for 6 months, albumin concentration varied only from 4·5 to 5·3 g., fibrinogen from 0·3 to 0·45 g., beta-gamma globulin from 1·3 to 2 g., and alpha globulin fraction from 0·7 to 1 g. per 100 ml. In all six cases of rheumatic fever alpha-globulin and fibrinogen concentrations were found to be significantly elevated and, conversely, that of albumin depressed during the acute phase of the attack. The degree of protein alteration and duration of the abnormal pattern paralleled the severity of the rheumatic process. The E.S.R. and C-reactive protein concentration tended to return to normal levels before the alpha-globulin fraction as revealed by the cationic detergent technique. The author concludes that cationic detergent fractionation is a more sensitive index of inflammatory activity than the other two methods referred to. *D. Preiskel.*

Comparative Action of Hormones and Salicylates in the Treatment of Acute Articular Rheumatism in Children. (Traitement du rhumatisme articulaire aigu chez l'enfant. Action comparée du traitement hormonal et du traitement salicylé.) MARQUÉZY, R. A., DI MATTEO, J., BACH, C., and SCHRUB, J. (1956). *Sem. Hôp. Paris*, **32**, 1115. 16 figs, 11 refs.

The effects of ACTH (corticotrophin), cortisone, and hydrocortisone in the treatment of acute rheumatism in children were compared at the Hôpital Trousseau, Paris, 87 patients being treated for 100 attacks, of which 61 were treated with ACTH by injection, 24 with cortisone by mouth, and fifteen hydrocortisone by mouth. The daily dosage of ACTH was 50 to 100 mg., that of cortisone about double this amount, and that of hydrocortisone slightly less. No significant difference was observed between the three types of treatment, the duration of which varied greatly, but except in severe cases or those with carditis a "short" course of treatment lasting 15 to 20 days appeared to be as effective as a longer course. The effect of the hormones was most striking in cases of pericarditis. In children in whom the myocarditis dominated the picture the effect was less marked, and in those in whom endocarditis was predominant the effect was difficult to evaluate.

The results obtained with hormone therapy were compared with those obtained in 128 cases treated previously with sodium salicylate. The temperature and erythrocyte sedimentation rate returned to normal more rapidly on the whole on the hormone-treated cases (though in a small group of cases (eighteen) treated with acetylsalicylic acid the effect on fever and arthritis was comparable with that of cortisone). In some cases treated with hormones, however, after the initial fall in temperature a slight rise was noted, which might persist for several weeks without other signs of progressive disease. The authors distinguish this from the rebound phenomenon, which occurred in about half the cases when treatment was stopped or the dose reduced. It was difficult to compare accurately the effects on the course of the carditis, but fourteen of the 128 patients treated with salicylates died within 12 months, compared with only one of the 87 treated with hormones. There was no marked difference in the development and persistence of valvular lesions between the two groups. Hormone therapy did little to reduce the incidence of subsequent relapses, which occurred in about one-third of the cases.

[It should be noted that the two series were not strictly comparable, as they were not treated simultaneously.]

C. Bruce Perry.

Prevention of Recurrent Rheumatic Fever: the Use of Repository Benzathine Penicillin G. DIEHL, A. M., HAMILTON, T. R., and MAY, J. S. (1956). *Sth. med. J.* (*Bgham, Ala*), **49**, 250. 3 figs, 17 refs.

With the object of preventing a recurrence of rheumatic fever, 118 children suffering from the disease at the Children's Convalescent Center, Kansas City, were each given 1,200,000 units benzathine penicillin intramuscularly every 28 days for periods varying from 6 to 32 months. Nose and throat swabs were examined just before the injection was given and also during acute respiratory infections with fever or sore throat. When β-haemolytic streptococci were isolated initially a second specimen was cultured within 48 hrs of the injection. Throughout the investigation the organisms were grouped according to Lancefield's system. Just before each injection blood was withdrawn for the determination of the antistreptolysin-O titre.

Of 79 nose and throat swabs cultured before prophylactic injection five were positive for β-haemolytic streptococci, and of 2,738 cultured afterwards, 49 (1·8 per cent.) were positive, the organism in thirteen of these belonging to Lancefield Group A. In only five instances were the follow-up cultures positive. In one case streptococci persisted for 11 days after the injection, and the prophylactic treatment had to be augmented with injections of procaine penicillin. The antistreptolysin-O titre was determined on 2,546 occasions; a significant rise in titre from previous levels was observed in seven instances, in three of which the rise immediately followed the start of prophylactic treatment and in four it occurred several months later. In none of these cases had a positive culture been obtained one or 2 months earlier. In one case a titre of over 500 units persisted for 11 months.

A total of 3,235 injections of penicillin were given without serious complications. An erythematous, macular, rash developed in three patients one to 12 days after the injection but was only temporary, and one child had polyarthralgia as well. The injections were continued in these patients without further reactions, except for the recurrence of the rash in one. Pain at the site of the injection was common and was occasionally associated with limping.

There was no relapse of rheumatic fever during the period of observation. The authors consider that prophylaxis is more certain with intramuscular injection than with oral administration because adequate blood levels are maintained more continuously and there is no doubt that the patients actually receive the drug prescribed.

John Lorber.

Relationship of Immune Response to Group-A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever. STOLLERMAN, G. H., LEWIS, A. J., SCHULTZ, I., and TARANTA, A. (1956). *Amer. J. Med.*, **20**, 163. 4 figs, 15 refs.

The authors have attempted to clarify the problem of whether recurrences of rheumatic fever are due to repeated subclinical streptococcal infection, by relating the immune response to such infection to the clinical course of the disease. In a series of 580 patients with rheumatic fever at Irvington House Hospital, Irvington-on-Hudson, New York, cultures of throat swabs were made and serial determinations of titres of antistreptolysin O, antistreptokinase, and antihyaluronidase performed at weekly intervals. During the first year of the study chemotherapy was given only when definite infection was confirmed, but during the last 3 years continuous chemoprophylaxis was administered to all the patients.

Within one month of onset of the disease nineteen (95 per cent.) of twenty patients showed an antistreptolysin-O titre of over 200 units, and at 2 months 66 out of 88 patients (78 per cent.) did so. Antihyaluronidase and antistreptokinase titres showed elevation in a rather smaller percentage of cases, but at 2 months 9·5 per cent. of the patients showed elevation of at least one of the antibody titres. The level or the rate of decline of the titre showed no relationship to the severity of disease. There were 461 patients in the series who had experienced only a single attack of rheumatic fever.

In 25 of the cases in which the disease ran a course of more than 6 months the same progressive decline in antibody level was observed as in the more acute cases. When a relapse occurred more than 8 weeks after the withdrawal of antirheumatic treatment with aspirin or cortisone, it was always associated with demonstrable evidence of new streptococcal infection. Isolated cases of chorea or erythema marginatum as late manifestationi were not associated with fresh streptococcal episodes ns this study.

The authors consider that immunological evidence of antecedent streptococcal infection can be found in every new attack of rheumatic fever.

G. Loewi.

Antistreptolysin-O Titre in Rheumatic Fever in Children treated with Cortisone and Prednisone. (Il titolo O-antistreptolisinico nella malattia reumatica dell' infanzia trattata con cortisone e prednisone.) LANZA, I., MORBIDELLI, R., and PAPOTTI, G. (1956). *Minerva med. (Torino)*, **1**, 553. 1 fig., 33 refs.

The effects of cortisone in high and in low dosage and of prednisone on the serum titre of antistreptolysin-O in 21 patients aged 5 to 13 years with rheumatic fever were studied at the Ospedale Maria Vittoria, Turin. In addition to hormone therapy, chemotherapy and salicylates were given in some cases, neither of which exerts any influence on the antistreptolysin-O titre. High-dosage cortisone treatment began with 150 to 200 mg. daily for 3 days, then 125 mg. daily for 5 to 7 days, followed by 75 mg. daily, the total period of treatment being 2 to 6 weeks. For low-dosage cortisone treatment 1 to 3 mg. per kg. body weight was given intramuscularly daily divided in two or three doses. Prednisone was given in a dosage of 0·5 to 1 mg. per kg. daily by mouth divided into three or four doses. Low-dosage cortisone and prednisone were given in repeated courses of 15 to 25 days' duration according to clinical requirements. The numbers of patients receiving the three treatments were three, ten, and eight respectively.

The antistreptolysin-O titre was determined before treatment in all cases and again every 8 to 18 days for a total of 40 to 70 days. In the group receiving high-dosage cortisone the titre returned to normal in 30 to 45 days, whereas in the other groups it fell more gradually and slowly, returning to normal in 35 to 70 days. Without hormone treatment the antistreptolysin-O titre remains elevated for 4 to 6 months.

The initial antistreptolysin-O titre and the rate of change did not appear to be related to the clinical severity of the disease. The erythrocyte sedimentation rate on the other hand more closely reflects the clinical state, but is not so specific and gives no indication of the level of antibody formation. *F. Hillman.*

Studies in Rheumatic Fever. JOHNSTON, J. A. (1956). *A.M.A. J. Dis. Child.*, **91**, 250. 12 figs, 20 refs.

Of 230 children with rheumatic fever seen between 1928 and 1949 at the Henry Ford Hospital, Detroit, there was a correlation between their nutritional status on admission (as judged by their position on the Wetzel grid) and the outcome. Of 164 with average or better nutrition the outcome was "satisfactory" (no carditis or no functional handicap) in 138, whereas of 66 with nutrition below average the outcome was satisfactory in only forty. The outcome was "unsatisfactory" (functional handicap or death) in 26 in each group. The outcome in children on an inadequate diet was somewhat less favourable than in those on a good diet.

Nitrogen and calcium balance studies carried out on thirty children during treatment with cortisone or corticotrophin showed large losses of nitrogen during the first 10 days, but the effect on calcium balance was not consistent. On hormone withdrawal there was a rapid rebound of storage of nitrogen. Prolonged bed rest adversely influenced the retention of nitrogen and calcium, but even very moderate degrees of activity offset this tendency. On a regimen of combined cortisone, salicylates, and ascorbic acid significantly better results were obtained than in a series of cases treated in the preceding 10 years, but a general decline in the severity of this disease may have contributed to this effect. *John Lorber.*

Clearing Factor in Rheumatic Fever. (Le facteur d'éclaircissement dans la maladie de Bouillaud.) KAUFMANN, H., DOURDOU, G., LYON, D., PAYOT, J., and ISORNI, P. (1956). *Arch. Mal. Cœur*, **49**, 147. 2 refs.

The absence of a lipid-clearing factor in the plasma of patients suffering from rheumatic fever has previously been pointed out by the first-named author (*Presse méd.*, 1955, **63**, 1045). In this paper from the Hôpital de Versailles further details of the potential clinical value of this phenomenon are presented on the basis of the investigation of 36 cases of acute rheumatic fever with joint involvement, the clearing factor being sought at the beginning of an acute attack, on the disappearance of physical signs, and during relapse. At the same time the concurrent changes in the erythrocyte sedimentation rate (E.S.R.), leucocyte count, antistreptolysin-O titre, and in the electrophoretic pattern of the plasma proteins were determined.

The clearing factor was found to disappear in all cases examined during the acute phase of the illness, and to reappear as soon as this phase began to subside. This process was more rapid in patients being treated with cortisone, than in those receiving salicylates and aspirin. In many cases the clearing factor disappeared before increases in the E.S.R., leucocyte count, or the plasma α-globulin level were detectable. Similarly, the reappearance of the factor was noted even before the onset of clinical improvement, and before any other changes in the laboratory tests, this finding being again particularly marked in patients receiving cortisone. During relapse a similar precocity of changes in the clearing factor was noted; thus in two cases in relapse the factor disappeared on the first day, whereas changes in the E.S.R. and protein electrophoretic pattern only appeared on the third day. In some cases the disappearance of the clearing factor was noted as early as 24 hrs before the clinical appearance of a relapse.

Although the test for the lipid-clearing factor is not specific for rheumatic fever—similar changes having been noted in some types of anaemia, acute pulmonary states, and certain neurological and endocrine conditions [not specified]—the authors suggest that as the test is simple and useful diagnostically, it should prove of value as a routine measure once the practical difficulty of providing a lipid substrate which will give consistent results can be overcome. *P. I. Reed.*

Results of Cortisone and ACTH Treatment of Rheumatic Fever. HECHT, M. S., SHELDEN, W. E., NOLKE, A., HOFSTRA, D., and WEST, E. (1956). *J. Pediat.*, **48**, 300. 16 refs.

Cortisone and ACTH were given in the treatment of 122 cases of rheumatic fever admitted to the Childrens'

Hospital of Michigan, Detroit, between April, 1950, and September, 1953. All the patients, who were under 12 years of age, were followed up for at least one year after cessation of treatment. Details are given of the dosages of the drugs and of other forms of therapy employed. Some signs of the Cushing syndrome were observed in most cases during treatment and transient glycosuria and hypertension were noted in a few. In some cases chicken pox, mumps, and measles developed, but these diseases ran their usual courses. The duration of treatment did not exceed 12 weeks, except in three cases. In 24 cases valvular lesions disappeared. The size of the heart decreased in 25 cases and increased in seven. There were three deaths in the series, and in sixteen cases there was a recurrence of rheumatic activity.

These results were compared with those obtained in a similar group of cases of rheumatic fever admitted to the same hospital between December, 1946, and April, 1950 and treated with salicylates. Signs of valvular lesions disappeared in only three cases in the latter series and there were fifteen deaths. It is concluded that although hormone therapy does not cure rheumatic fever it is useful in suppressing the inflammatory reactions which occur during rheumatic activity. *Kathleen M. Lawther.*

Unusual Changes in the Pericardium in Rheumatic Fever. (Singolari alterazioni della sierosa pericardica nell' infezione reumatica.) SANNAZZARI, G. L., and VISIOLI, O. (1955). *Riv. Anat. patol.*, **10**, 595. 11 figs, 35 refs.

Appraisal of Certain Acute Phase Reactants in a Single Blood Sample and their Value in the Diagnosis of Acute Rheumatic Fever. ADAMS, F. H. (1956). *J. Pediat.*, **49**, 16. 2 figs, 21 refs.

Statistical Study of Rheumatic Fever in Infancy. (Contributo allo studio statistico della malattia reumatica nell'infanzia.) LANZA, I., and MORBIDELLI, R. (1956). *G. Batt. Immun.*, **49**, 117. Bibl.

Mechanism of Death in Rheumatic Heart Disease in Different Age Periods. WALLACH, J. B., LUKASH, L., and ANGRIST, A. A. (1956). *Amer. J. clin. Path.*, **26**, 360. 2 figs, 7 refs.

Antistreptolysin-O Titre as an Index of Rheumatic Activity in Stabilized Valvular Disease. (Il titolo della anti-O-streptolisina come indice di attività reumatica nei vizi valvolari siabilizzati.) BASEVI, A., and TOSO, M. (1956). *G. Clin. med.*, **37**, 506. 5 figs, bibl.

Infective Nephritis and Rheumatic Fever. (Néphrites infectieuses et maladie de bouillaud.) LUTEMBACHER, R. (1956). *Presse méd.*, **64**, 1047.

Use of Aspirin in the Treatment of Rheumatic Fever. (Utilisation de l'aspirine dans le traitement du R.A.A.) MOZZICONACCI, P., and MANUEL, J. (1956). *Bull. Soc. méd. Hôp. Paris*, **4**, 389. 1 fig.

Contribution to the Study of Juvenile Rheumatism; Ankylosing Spondylitis in Childhood. (Contribución al estudio del Reumatismo Infantil Espondilitis Reumatoidea Anquilosante de la Infancia.) LUCCHESI, M., and LUCCHESI, O. (1956). *Rev. argent. Reum.*, **21**, 18. 8 figs, 6 refs. Also *Reumatismo*, **8**, 130.

Streptococcal Agglutination and the Indirect Lysis of Erythrocytes in Rheumatic Fever. (L'agglutinazione streptococcica e la lisi mediata degli eritrociti nella febbre reumatica acuta.) CARCASSI, U., and PORCELLI, M. (1956). *Reumatismo*, **8**, 137. 8 refs.

Chemotherapy of Rheumatic Fever. CLARKE, N. E., CLARKE, C. N., and MOSHER, R. E. (1956). *J. Mich. med. Soc.*, **55**, 517.

Blood Groups and Disease: Rheumatic Fever. WALSH, R. J., and KOOPTZOFF, O. (1956). *Aust. Ann. Med.*, **5**, 17. 11 refs.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Results of Long-Term Treatment of Rheumatoid Arthritis. An Attempt at a Comparative Evaluation of Cortisone and Corticotrophin Therapy. JORDAL, R. (1956). *Dan. med. Bull.*, **3**, 24. 3 figs, 15 refs.

At Frederiksborg County Central Hospital, Hillerod, Denmark, 45 patients with rheumatoid arthritis and three patients with ankylosing spondylitis were given long-term treatment with ACTH (corticotrophin) in doses ranging from 3·3 to 20 units daily. At the end of 6 months the results were regarded as satisfactory in 34 cases (73 per cent.), but after a further 6 months the proportion had fallen to 56 per cent. Treatment was stopped before the end of the course in four cases because a sustained remission was obtained, and in eleven cases because it had ceased to be effective. In six others treatment had to be stopped because of serious side-effects.

The authors point out that for long-term treatment ACTH has the advantage over cortisone that adrenal involution is avoided, so that the risk of adrenal failure due to stress either during or after treatment is absent. Moreover, a number of the in-patients who stopped the injections abruptly, contrary to instructions, suffered no ill-effects such as are seen on sudden withdrawal of cortisone. They point out, however, that there is some variation in the potency of ACTH from different sources and also from batch to batch from the same source. On the whole they consider that ACTH is preferable to cortisone for long-term treatment, but they emphasize that the dose should be as small as possible.

Oswald Savage.

Liver Function Tests in Rheumatoid Arthritis. DARBY, P. W. (1956). *J. clin. Path.*, **9**, 153. 2 figs, 35 refs.

Numerous attempts have been made to demonstrate an impairment of liver function in association with rheumatoid arthritis. The present author's contribution is particularly concerned with the results of the "bromsulphalein" retention test, the coproporphyrin urinary

excretion test, and various flocculation tests and with the serum bilirubin level and urinary urobilinogen excretion in this disease. The tests were carried out at the Westminster Hospital, London, on fifty cases of rheumatoid arthritis and a control series of 45 patients with other diseases, the groups being similar in age and sex distribution and in the proportion of ambulant cases which they contained.

In eleven out of 47 cases of rheumatoid arthritis dye retention was 10 per cent. or more 30 min. after an intravenous injection of 5 mg. bromsulphalein per kg. body weight, whereas only in two of the 44 control subjects tested was there retention to this degree. This difference is shown to be statistically significant. The urinary coproporphyrin excretion was studied because of its sensitivity as an index of liver function. The coproporphyrin content of afternoon collections of urine over a 2-hr period from 26 healthy subjects showed the normal value to be less than 20 μg.

Of 49 patients with rheumatoid arthritis, fifteen showed an excretion in excess of this value, compared with only two of the 41 in the control group. Statistical analysis again shows this difference to be highly significant. The serum bilirubin and urinary urobilinogen levels were within the normal range in both groups and the results of the flocculation tests were inconclusive. These results are held to confirm that in a proportion of cases of rheumatoid arthritis (between one-quarter and one-third of the present series) there is evidence of some impairment of liver function. The degree of impairment in such cases could not be correlated with the severity or duration of the rheumatoid condition, nor was impairment less common in treated than in untreated cases. [While not entirely consistent with the findings reported in the very many other papers on this subject, the conclusions reached in this paper seem to be derived from a very fair assessment of the facts observed.] *Harry Coke.*

Clinical Significance of Histological Amyloid in Rheumatoid Arthritis. [In English.] LAINE, V., MÄKINEN, P., MÄKINEN, G. L., HOLOPAINEN, T., and SAIRANEN, E. (1956). *Acta rheum. scand.*, **1**, 257. 1 ref.

In a previous report from the Hospital of the Rheumatism Foundation, Heinola, Finland, the authors described the occurrence of amyloid-like material in 50 per cent. of biopsy specimens of various tissues (but mainly the skin) in patients suffering from rheumatoid arthritis. They now report an attempt to correlate the biopsy findings with the clinical features in 100 unselected cases of rheumatoid arthritis, 37 in men and 63 in women. The degree of the amyloid change tended to be more pronounced in severe cases of rheumatoid arthritis, but no definite correlation was obtained with sex, age, or duration of the disease. *R. E. Tunbridge.*

Clinical Evaluation of Prolonged ACTH and Cortisone Therapy in 114 Cases of Rheumatoid Arthritis. [In English.] SOLEM, J. H., and RÖMCKE, O. (1956). *Acta rheum. scand.*, **1**, 243. 10 refs.

A report is presented, from Drammen Hospital, Drammen, Norway, of the results of a 3½-year study of 208 patients with rheumatoid arthritis, of whom 114 were found suitable for prolonged hormone therapy. ACTH (corticotrophin) was given in the form of the long-acting gel base in a dose of 20 units three times a week. Other patients received cortisone, 50 mg. per day, the longest period of treatment up to the end of the survey being 25 months. There was satisfactory improvement in 30 per cent. of the patients; the usual side-effects were noted, but none were fatal. The authors stress that this type of long-term therapy is suitable for only a small proportion of patients—in the present series it amounted to 16 per cent. *G. S. Crockett.*

Active Immobilization of Joints in Rheumatoid Arthritis. KELLY, M. (1956). *N.Z. med. J.*, **55**, 11. 4 figs, 4 refs.

It is pointed out that rheumatoid arthritis is a disease of movement and that if there were no movement there would be no disease. Control of movement, therefore, becomes the most important of all therapeutic measures in the management of cases of rheumatoid arthritis. The author advocates active immobilization by splinting a painful joint and allowing the patient to use the limb. The wrists and elbows may be immobilized in plaster for approximately 4 weeks, then gradually mobilized. The shoulder should be immobilized by strapping the arm and forearm to the chest wall for 3 weeks. For the knee immobilization in a band caliper for 4 weeks is preferred, walking being encouraged. Manipulation under anaesthesia may be necessary to correct a flexion deformity of the knee; this is followed by immobilization in a splint.

The author emphasizes that immobilization by splinting for a few weeks is not followed by ankylosis if the joint cartilage is intact. Immobilization allows the swelling to subside and facilitates the return of a good range of movement. If the cartilage is disorganized a stable arthrodesis is a good result. *J. B. Millard.*

Correlation between Biopsy Findings and the Congo Red Test in Rheumatoid Arthritis. [In English.] SAIRANEN, E., KOSKINEN, H. M., and HOLOPAINEN, T. (1956). *Acta rheum. scand.*, **1**, 262. 7 refs.

In forty cases of rheumatoid arthritis in which amyloid change had been demonstrated in biopsy specimens, mainly of the skin and synovial membranes, at the Hospital of the Rheumatism Foundation, Heinola, Finland, the authors carried out a modified form of the Bennhold test for amyloidosis. With the patient fasting, 1·5 ml. of a 10 per cent. solution of Congo red per 10 kg. body weight was injected intravenously and blood samples taken after 3 and again after 60 min., the proportion of the injected dye removed from the blood after 60 min. being calculated from the results of spectrophotometric examination of these and a blank sample taken before the injection. The mean proportion of Congo red disappearing from the blood in the patients with rheumatoid arthritis was 48 per cent. compared with 33 per cent. in 21 healthy adults. Moreover, the figure was above 40 per cent. in 24 of the former and in only one of the latter. Although the individual figures in the former group varied widely without relation to the biopsy

findings it is concluded that enough amyloid-like material is present in various tissues in certain cases of rheumatoid arthritis to affect the result of the Congo-red test.

R. E. Tunbridge.

Case of Still's Disease with Ocular Complications. (Un cas de maladie de Still, compliqués de manifestations oculaires.) ZARRABI, M., and PARHAMI, Y. (1956). *Arch. Ophtal.*, **16**, 177.

The patient was an under-nourished child of 8 years of age. The liver and spleen were enlarged, and the right knee swollen, deformed, and painful, but the other joints were normal. Other features were enlargement of inguinal cervical and axillary lymph nodes, a papular rash on the legs, periodic bouts of fever, and a raised erythrocyte sedimentation rate.

There was symmetrical band-shaped opacity of the corneae. The pupils were occluded by fibrous tissue, the vision of the better eye amounting only to ability to count fingers. The eyes were irritable and there was pericorneal injection.

Treatment by cortisone systemically and locally resulted in a striking improvement both in the general and in the ocular condition; but the liver and spleen remained enlarged and other manifestations of disease returned from time to time so that the future course is uncertain.

A. A. Douglas.

Quantitation of the Activity of Rheumatoid Arthritis. (A Method for Recording its Systemic Manifestations.) LANSBURY, J. (1956). *Amer. J. med. Sci.*, **231**, 616.

The inadequacy of existing methods of recording the activity of patients suffering from rheumatoid arthritis is stressed. A clear distinction is made between assessments which concern themselves only with the state of joint activity and those in which the systemic manifestations are stressed. It is pointed out that the former is extremely time-consuming and demands much skill and experience on the part of the assessor. It is therefore impracticable as a routine procedure.

For routine and rapid assessments, the author recommends in the first place a record of systemic manifestations, such as fever, loss of weight, erythrocyte sedimentation rate, anaemia, reversed albumin/globulin ratio, and C-reactive protein.

Some effort to estimate the symptomatology is also advocated in order to render the patients' descriptions more reliable. The suggestion is that patients should be asked about the *duration* rather than the intensity of their symptoms.

A routine record is also made of pain at rest, pain on motion, morning stiffness, "jelling" (*i.e.* stiffness after rest), fatigue (including the number of hours the patient can work), salicylate consumption, and weakness (as measured by certain functional tests).

Of these criteria, the author has found pain at rest and pain on motion to be useful guides but difficult to quantitate. By contrast, morning stiffness and diurnal "jelling" are simple to evaluate according to their duration and it is claimed that their values diminish regularly as patients go into remission.

A proforma is suggested which can be stamped into the patient's notes at each visit, and the author claims that with its help he takes only 3 to 5 minutes to record the necessary data. As with any other system, more consistent results are obtained with early than with advanced cases. In patients undergoing treatment with steroids, the information must be regarded rather as a measure of the efficacy of the drug than of the state of the underlying disease activity.

[The paper abstracted above appears to be the first of a series of five articles. In the remainder—which will be reviewed in a later issue—the author analyses in detail and then integrates each of the criteria which he recommends into a composite scheme.] *J. H. Glyn.*

Rheumatoid Arthritis. A Disease Entity or Only a Symptom? (Die primär chronische Polyarthritis, ein einheitliches Krankheitsbild, oder nur ein Symptom?) BÖNI, A. (1956). *Bull. schweiz. Akad. med. Wiss.*, **12**, 93. 5 refs.

Involvement of the Hip in Rheumatoid Arthritis. (Les atteintes de la hanche au cours des polyarthrites chroniques évolutives.) PIGUET, B. (1956). *Sem. Hôp. Paris*, **32**, 2483. 10 figs, 11 refs.

Rheumatoid Arthritis in the Elderly. DORDICK, J. R. (1956). *J. Amer. Geriat. Soc.*, **4**, 588. 6 refs.

Treatment of Severe Chronic Articular Rheumatism with Prednisone. (Zur Behandlung des schweren chronischen Gelenkrheumatismus mit Prednison (Decortin).) KLEINSCHMIDT, T. (1956). *Medizinische*, **29**, 1036. 10 refs.

Treatment of Rheumatoid Arthritis by the Arterial Route after Several Years' Experience. (Le traitement par voie artérielle de la polyarthrite chronique évolutive après quelques années d'expérience.) DEBRAY, M., and LANTY, R. (1956). *Presse méd.*, **64**, 1061.

Visceral Lesions in Rheumatoid Arthritis. [In English.] SKOGRAND, A. (1956). *Acta rheum. scand.*, **2**, 17. 3 figs, 36 refs.

Intracutaneous Congo Red Test in Cases of Rheumatoid Arthritis. [In English.] LAINE, V., HOLOPAINEN, T., and MÄKINEN, P. (1956). *Acta rheum. scand.*, **2**, 31. 1 fig., 4 refs.

Biological Syndrome of Chronic Inflammatory Rheumatism. I. A Critical Study and Evaluation of the Waaler-Rose Reaction in the Diagnosis of Rheumatoid Arthritis. (Le syndrome biologique des rhumatismes chroniques inflammatoires. I. Etude critique et valeur de la réaction dite de Waaler et Rose dans le diagnostic de la polyarthrite chronique évolutive.) DULONG DE ROSNAY, C., and DU PASQUIER, P. (1956). *J. Méd. Bordeaux*, **133**, 548. 28 refs.

Electrophoresis in Rheumatoid Arthritis. HOULI, J., and HASSON, A. (1956). *Rheumatism*, **12**, 52. 3 figs, 11 refs.

Clinical Experience of the Use of Prednisone combined with Diacetyl-3-Carboxyl Acid in Rheumatoid Arthritis. (Esperienze cliniche con l'associazione prednisone-acido diacetil-3-carbossilico nell'artrite reumatoide.) GALLI, T., and SOLARI, S. (1956). *Reumatismo*, **8**, 227. 7 refs.

(Osteo-Arthritis)

Useful Preparation in the Treatment of Osteo-Arthritis. WILKINSON, L. H. (1956). *Rheumatism*, **12**, 63. 23 refs.

(Spondylitis)

Natural History of Rheumatoid Spondylitis. BLUMBERG, B., and RAGAN, C. (1956). *Medicine (Baltimore)*, **35**, 1. 10 figs, bibl.

A detailed account of the natural history of "rheumatoid" (ankylosing) spondylitis is presented, based on a study of those cases in which the diagnosis was made at the Presbyterian Hospital, New York, between 1928 and 1954. The total number of patients concerned was 311, of whom 102 attended for follow-up examination for the purposes of this study, forty responded to an inquiry by letter, and fourteen were reported to be dead, while the remainder could not be traced. Males constituted 80 per cent. of the patients and females 20 per cent.; the average age of onset was 27 years.

In evaluating the status of the disease in each case followed up attention was directed to:

(1) functional ability,
(2) pain,
(3) physical deformity,
(4) *x*-ray changes,
(5) laboratory findings.

Functional ability was determined along the lines suggested by the American Rheumatism Association for rheumatoid arthritis: of 121 patients followed up 2 to 35 years after the onset of the disease, 76 per cent. were placed in Class 1, leading "essentially normal occupational lives", and only 4 per cent. in Class 4, leading a "bed and chair existence". The ability to work was found to be remarkably well maintained, on the average, until the age of 55 years. Severe hip involvement was the cause of poor functional ability in twelve of the 24 cases in Classes 2, 3, and 4, spinal deformity alone being rarely responsible. Pain was greatest in the early, acute phase of the disease and tended to decrease or even disappear in later years.

The degree of physical deformity of the spine progressed relentlessly with the duration of the disease, though it did not necessarily become very severe. Only 30 per cent. of the patients had peripheral joint involvement at the time of examination, although 67 per cent. had had such involvement in the past. All the patients examined had a reduced chest expansion, which was less than 0·5 cm. in 60 per cent. There was a history of iritis in 25 per cent. The erythrocyte sedimentation rate was normal in 20 per cent. of the patients at the time of examination, but it tended to be elevated in the acute phase of the disease. In only one case was the streptococcal agglutination reaction positive, and there was none in which the Waaler-Rose test gave a positive result. *X*-ray changes in the spinal diarthrodial joints and sacro-iliac joints and paravertebral calcification appeared to proceed unremittingly with the passage of time.

C. E. Quin.

(Miscellaneous)

Clearance of Radioactive Sodium from the Knee Joint. HARRIS, R., and MILLARD, J. B. (1956). *Clin. Sci.*, **15**, 9. 6 figs, 5 refs.

At the Devonshire Royal Hospital, Buxton, Derbyshire, the authors have carried out a quantitative study of the local circulation in the knee-joint of twenty healthy subjects by determining the clearance of radioactive sodium (^{24}Na) measured with unshielded scintillation counters at one-min. intervals up to one hr after the injection of 5 to 10 microcuries ^{24}Na in isotonic saline solution into the knee joint. The results were plotted semi-logarithmically against time and showed that the clearance from the joint was exponential; the mean clearance constant (K) in 23 tests was found to be $0{\cdot}050 \pm 0{\cdot}021$.

Arterial occlusion in the thigh by means of a cuff at a pressure of 200 mm. Hg completely inhibited clearance, while venous occlusion at a pressure of 60 mm. Hg effected a significant decrease in the rate. Light, non-weight-bearing exercise was followed by a decrease in clearance, while heating of the knee-joint by short-wave diathermy, producing an elevation of the intra-articular temperature of 3° to 6° C., increased the rate of clearance by 100 per cent.

The authors consider that the technique and the method of assessment by the clearance constant give accurate and sensitive results and, moreover, are suitable for the study of local circulatory changes within the knee-joint.

Harry Coke.

Zoxazolamine (Flexin) in Rheumatic Diseases. SMITH, R. T., KRON, K. M., PEAK, W. P., and HERMANN, I. F. (1956). *J. Amer. med. Ass.*, **160**, 745. 3 refs.

Zoxazolamine is a muscle relaxant which acts centrally on polysynaptic pathways and has virtually no effect on distal structures. It was tried at the Pennsylvania Hospital, Philadelphia, in 95 cases of rheumatic disease in which painful muscle spasm was a prominent feature, the dosage being 750 to 2,000 mg. daily. The response was excellent in 41 and good in 44 cases, muscle spasm being greatly relieved. Of sixteen patients with ankylosing spondylitis fifteen were able to perform exercises, morning stiffness being quickly relieved by the first dose. In other groups of patients, chiefly those with "fibrositis", cervical root syndrome, and rheumatoid arthritis, there was similar but less marked relief. Toxic reactions were noted in 43 cases, and necessitated discontinuance of treatment in thirteen. The commonest were disturbances of the gastro-intestinal tract and of equilibrium. In 21 patients toxic effects were eliminated when the dosage was reduced by one-half. Zoxazolamine was also given to five patients with little muscle spasm, but they did not appear to benefit.

The authors consider that Zoxazolamine, because of its effectiveness in relieving spasm and the mildness and controllability of its side-effects, is the best muscle relaxant they have yet tried. *B. E. W. Mace.*

Value of Physiotherapy in Rheumatic Diseases. I. Palliation. LAWRENCE, J. S., and SLADDEN, R. J. (1955). *Ann. phys. Med.*, **2**, 282. 2 figs, 8 refs.

An attempt was made at the Walkden Clinic, Manchester, to assess the relative values of eleven different physiotherapeutic procedures in the relief of pain in chronic rheumatic disorders, including short-wave diathermy, ionization, radiant heat, infra-red, ultraviolet, and ultra sound irradiation, traxator, and wax baths, treatment being followed by massage. Skin and deep-tissue temperatures were determined before and after treatment. The results showed that the greatest relief was obtained with short-wave diathermy but that the effect of histamine ionization was more prolonged. Massage augmented both the degree and duration of the relief.

It is concluded from temperature measurements that short-wave diathermy acts mainly by deep heating, whereas histamine ionization produces its effect by skin stimulation. *Kathleen M. Lawther.*

Rheumatic Origin of Inflammations of the Uvea. (Zur Frage der rheumatischen Genese entzündlicher Erkrankungen der Uvea.) RINTELEN, F. (1956). *Bull. schweiz. Akad. med. Wiss.*, **12**, 156.

The significance of uveal inflammations is shown by the fact that in the Basle eye clinic uveitis ranks third in the cause of blindness. Of 1,500 out-patient clinic, 75 (5 per cent.) had to be admitted because of uveitis, and there is a larger number of cases treated in the out-patient department. Clinically, rheumatic iritis is not an entity and this group is more correctly called after Franceschetti "*du type rheumatismal*" and is usually unilateral, often recurring; often there is fibrinous exudate in the anterior chamber causing posterior synechiae and an increase of intra-ocular pressure. Keratic precipitate is not so marked. 75 per cent. are over 40 years of age. There is usually no temperature and in about half the cases the blood sedimentation rate is normal. The frequency of focal sepsis in those affected was not greater than that of a similar age group without eye complaints. The Mantoux reaction was usually positive 1 in 10,000 or 1 in 1,000, but there was no focal reaction in the eye. It is important that both in the granulomatous and in the five times more frequent diffuse exudative form of anterior uveitis, the general condition of the patient gives very little information. Rheumatic arthritis was present only in about ten cases in the author's group. The increased erythrocyte count cannot be regarded as a pointer to a rheumatic aetiology of uveitis. Uveitis of course may be of rheumatic origin just as it may be of a tuberculous origin but in both cases the association of the uveitis with the disease is difficult to prove. The Middlebrook-Dubos agglutination test in the aqueous, and the streptolysin blood test are not proofs. In most cases the aetiology remains obscure. The favourable results of treatment with cortisone points to an allergic pathogenesis. A follow-up of former iritis patients should help in clarifying the aetiology and pathogenesis of uveitis. *M. Klein.*

Objections to the Concept of Salicylate Therapy as a Stimulant of Hormone Production. (Que peut-on objecter au concept: Salicylothérapie médication hormonopoïétique?) ROSKAM, J. (1956). *Bull. schweiz. Akad. med. Wiss.*, **12**, 120. 10 figs, 32 refs.

Effects and Mode of Action of Radiotherapy in Rheumatic Affections. (Effets et mode d'action de la radiothérapie des affections rhumatismales.) COSTE, F., and FAURÉ, C. (1956). *Sem. Hôp. Paris*, **32**, 2491. 42 refs.

Rheumatism of Endocrine Origin. (Los reumatismos Endocrinos.) MARAÑÓN, G. (1956). *Clín. y Lab.*, **62**, 1.

Infective Foci and Rheumatic Diseases. (Foci infettivi e malattie reumatiche.) DE VECCHIS, B. (1956). *Policlinico, Sez. prat.*, **63**, 983.

Evaluation of Combined Prednisolone-Aspirin Therapy in the Treatment of Arthritis. SZUCS, M. M., HOLONKO, V., FORSTER, K. M., and NALAGAN, D. (1956). *Ohio St. med. J.*, **52**, 722. 5 refs.

Treatment of Certain Rheumatic Conditions with Trypsin. (Experiencia personal del tratamiento de algunos procesos reumàticos con tripsina.) SANS SOLÁ, L., and BARCELÓ, P. (1956). *Rev. esp. Reum.*, **6**, 373. 14 refs.

Action of Gold Salts per Rectum in Experimental Arthritis. (Azione dei sali d'oro per via rettale nell'artrite sperimentale.) FARNETI, P., and MICCOLI, G. (1956). *Reumatismo*, **8**, 142. 8 figs, 9 refs.

Rheumatic Diseases in the Works of Galen. (Las afecciones reumaticas en la obra de galeno.) RUIZ MORENO, A. (1956). *Arch. argent. Reum.*, **19**, 25.

Syndroma Reiter. [In English.] LÖVGREN, O. (1956). *Acta rheum. scand.*, **2**, 11. 6 refs.

Disk Syndrome

Injection of Hydrocortisone into the Spinal Canal in the Treatment of Lumbosciatica. (L'iniezione endorachidea di idrocortisone nel trattamento delle lombosciatiche.) BARBASO, E. (1956). *Reumatismo*, **8**, 92. 11 refs.

Pararheumatic (Collagen) Diseases

Discoid Lupus Erythematosus: An Analysis of its Systemic Manifestations. DUBOIS, E. L., and MARTEL, S. (1956). *Ann. intern. Med.*, **44**, 482. 18 refs.

In order to demonstrate that systemic changes are common in discoid lupus erythematosus the authors obtained a complete history and carried out physical examinations and laboratory investigations in 41 cases of the disease seen at the Los Angeles County Hospital, California. In 26 cases the discoid lupus was confined to the face, and in sixteen of them there was evidence some time during the illness of arthritis, fever, Raynaud's phenomenon, pleurisy, or other systemic changes. Generalized discoid lupus erythematosus was present in the remaining fifteen cases, in fourteen of which systemic changes developed. When those cases in which laboratory tests revealed leucopenia, an increased sedimentation rate, hyperglobulinaemia, and abnormalities in liver function were also considered, it was found that in 24 of the 26 cases of localized disease and in all fifteen cases of generalized disease there was evidence of systemic involvement. In three cases the result of the L.E.-cell test was positive 3, 5, and 10 years respectively after the onset of the disease.

The authors consider that the classification of lupus erythematosus is arbitrary and that the so-called discoid form is, from its inception, a systemic disease.

E. G. Rees.

Neuritis associated with Systemic Lupus Erythematosus. A Report of Five Cases, with Necropsy in Two. BAILEY, A. A., SAYRE, G. P., and CLARK, E. C. (1956). *A.M.A. Arch. Neurol. Psychiat.*, **75**, 251. 2 figs, 7 refs.

Since 1949 at the Mayo Clinic the authors have seen five cases of systemic lupus erythematosus associated with peripheral neuritis. In all the cases the presenting signs and symptoms were diagnostic of lupus erythematosus and on the whole the results of laboratory investigations were confirmatory. The response to the L.E.-cell test was positive in all five cases. The neurological manifestations varied in character and intensity, suggesting involvement of peripheral nerves, posterior root ganglia and the posterior column of the spinal cord, and focal cerebral damage with involvement of cranial nerve nuclei. The protein content of the cerebrospinal fluid was often greatly increased. Clinically, signs and symptoms mimicked those of the Guillain-Barré and the mononeuritis multiplex syndromes. Necropsy was performed in two cases; in one the vascular changes suggested periarteritis nodosa but the common lesion was intimal thickening. Changes in the central nervous system were scattered, consisting mostly in axis cylinder degeneration and demyelinization affecting peripheral nerves, posterior root ganglia, and posterior columns. In the authors' opinion it appeared unlikely that the nerve changes described could be accounted for by vascular degeneration alone.

[Experience suggests that the L.E.-cell test is not as specific as was thought. The absence, therefore, of definite vascular lesions to explain these rather bizarre neurological manifestations makes it difficult to accept them as part of the syndrome of systemic lupus erythematosus.] *J. N. Harris-Jones.*

Evaluation of Three Diagnostic Procedures for Systemic Lupus Erythematosus. HASERICK, J. R. (1956). *Ann. intern. Med.*, **44**, 497. 1 fig., 14 refs.

The author has compared the sensitivity and accuracy of the three techniques which have been devised for the demonstration of the cellular aggregation which constitutes the lupus erythematosus (L.E.) phenomenon—namely, using the patient's bone marrow, using peripheral blood, and by incubation of L.E. serum or plasma with normal (dog) bone-marrow cells *in vitro*—in cases of atypical systemic lupus erythematosus at the Cleveland Clinic, Cleveland, Ohio.

In 33 of a total of 79 cases the results of one or more of these three tests were positive, that with peripheral blood being positive in thirty, that with the patient's marrow in 24, and that with the patient's plasma and dog marrow in nineteen (the lower figure here, it is suggested, may have been due to the use of heparin). All three methods have advantages and disadvantages, and these are discussed; the test with peripheral blood is the most sensitive, but at the same time is the most difficult to interpret. On the whole the author considers the plasma–dog-marrow method to be the most suitable for the following reasons:

(1) it allows a control to be set up;
(2) the test can be repeated several times with one specimen of serum;
(3) the serum can be sent long distances for examination if local facilities are inadequate; and it is the most suitable method for research.

Replies to a questionary sent to twenty haematologists in different regions of the U.S.A. showed that all but one of them considered the L.E. tests to be specific for systemic lupus erythematosus. *E. G. Rees.*

Factors Influencing the Formation of L.E. Cells. A Method for Enhancing L.E. Cell Production. ZINKHAM, W. H., and CONLEY, C. L. (1956). *Bull. Johns Hopk. Hosp.*, **98**, 102. 5 figs, 12 refs.

In studies of the formation of L.E. cells *in vitro*, carried out at Johns Hopkins University School of Medicine, Baltimore, the authors have shown that the yield of L.E. cells from the blood of patients with systemic lupus erythematosus can be markedly increased if the blood is rotated in a flask containing glass beads during the incubation period. Experiments seemed to suggest that this is attributable to the effect of trauma on the leucocytes providing nuclear material for transformation, for as the degree of trauma to the leucocytes increased so, within limits, did the number of L.E. cells rise. The use of siliconed apparatus caused a marked reduction in L.E.-cell formation.

The authors also showed that large amounts of "extracellular material" may be produced by this

technique, and the studies would seem to confirm that this material is derived from injured or dead leucocytes and is the primary stage in L.E.-cell formation. When this technique was employed in studying the blood of a large number of patients with collagen-vascular diseases other than systemic lupus erythematosus no L.E. cells or "extracellular material" could be demonstrated.

E. G. Rees.

Treatment of Lupus Erythematosus with Mepacrine. CHRISTIANSEN, J. V., and NIELSEN, J. P. (1956). *Brit. J. Derm.*, **68**, 73. 5 figs, 23 refs.

The authors describe from the Finsen Institute, Copenhagen, the results achieved with mepacrine in the treatment of 97 cases of chronic lupus erythematosus all of the discoid or purely erythematous type. The drug was given initially in doses of 200 mg. daily, rising to 300 mg. until yellow pigmentation became marked (usually in about 21 days), and then reduced to 100 to 200 mg. daily; the mean total dose for the series was 18 g. given roughly at the rate of 1 g. per week. The period of follow-up ranged from 3 to 21 months (mean 9·7 months). The ratio of female to male patients was about 3 : 1. Little difference was observed between the results in the 56 patients treated in hospital and those (41) treated as out-patients.

There was an "excellent" result in one-third of the patients, and considerable improvement in a further third, the results being notably better in patients over 60 years of age. In both groups, however, there was a relapse rate of about 80 per cent. within a few months of stopping treatment. Side-effects occurred in 29 cases in the form of dyspepsia, dermatitis, and disorders of sweating, and necessitated suspension of treatment in twelve cases. The authors discuss their methods of evaluating improvement and subject their results to statistical analysis. (Since July, 1954, they have replaced mepacrine by chloroquine, and a report of the results with the latter drug is promised later.) *John T. Ingram.*

Histology of the Cutaneous Manifestations of Systemic Lupus Erythematosus. (Histologie des manifestations cutanées du lupus érythémateux systématisé.) PRUNIERAS, M. (1956). *Presse méd.*, **64**, 772. 16 figs, 40 refs.

Degradation of deoxyribonucleic acid in the nuclei of cells, with the formation of the so-called "red bodies", was demonstrated histochemically in sections of normal skin subjected to the action of depolymerizing agents and of the skin of patients with systemic lupus erythematosus not so treated. This phenomenon affects mainly the nuclei of lymphocytes and is then non-specific, occurring also in the discoid form of lupus erythematosus and in other conditions such as lichen planus and dermatomyositis. "Red bodies" derived from connective tissue cells, however, appear to be specific to systemic lupus erythematosus, and are related to the L.E.-cell phenomenon.

Other histopathological changes in the skin in lupus erythematosus discussed in this paper are:

(1) increased metachromasia to toluidine blue of the vascular walls, basal membranes (especially around the hair follicles), and of the basal substance, especially in the dermal papillae; staining with periodic-acid-Schiff reveals changes in the same situations;
(2) swelling and disruption of the basal membranes;
(3) increased phagocytic activity, especially on the part of histiocytes.

The author appears to be of the opinion that the so-called fibrinoid necrosis is a product, not of collagenous degeneration, but of nuclear degradation.

A. Swan.

Periarteritis Nodosa. Its Relationship to Endomyocardial Sclerosis. WATT, J., and LYNCH, J. B. (1956). *Lancet*, **1**, 658. 5 figs, 21 refs.

The authors report from Liverpool University the case of a boy aged 12 who in March, 1955, was admitted to hospital with a pyrexial illness which was thought to be due to a perinephric abscess and which responded favourably to treatment with penicillin and streptomycin; 4 months later, however, he died suddenly during the night, a few hours after complaining of mid-abdominal pain. Necropsy revealed endomyocardial sclerosis of the left ventricle, thrombosis of the splenic and the superior mesenteric arteries, old infarctions of the spleen, and early peritonitis. Typical lesions of acute periarteritis nodosa were found in the superior mesenteric artery, the aortic vasa vasorum, and the vessels of the pancreas and testes. The literature related to the association between endomyocardial sclerosis and periarteritis nodosa is reviewed, with particular reference to Loeffler's "endocarditis parietalis fibroplastica".

L. Crome.

Periarthritis of the Shoulder and the Shoulder-Hand Syndrome in Pulmonary Tuberculosis. (La periartrite della spalla e la sindrome spalla-mano in corso di tubercolosi polmonare.) EINAUDI, G. (1956). *Reumatismo*, **8**, 71. 21 refs.

Striated Muscle in the So-called Collagen Diseases. III. Histological Changes in Striated Muscle in Periarteritis Nodosa. (Il muscolo striato nelle cosiddette malattie del collageno. III: Le alterazioni istologiche del muscolo striato nella periarterite nodosa (P.N.).) BARBERA, V., and MALAGUZZI-VALERI, C. (1956). *Reumatismo*, **8**, 184. 51 figs, 30 refs.

Psychological Factors associated with Disseminated Lupus Erythematosus and Effects of Cortisone and ACTH. BRODY, S. (1956). *Psychiat. Quart.*, **30**, 44. Bibl.

General Pathology

Rapid Procedure for Erythrocyte Packed Cell Volume and Sedimentation Rate Determinations. RILEY, V., and VALLES, W. C. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 341. 8 figs, 7 refs.

In the interests of convenience, speed, and economy the authors, working in New York, have devised a new method of estimating the packed erythrocyte volume and the erythrocyte sedimentation rate (E.S.R.). For this relatively large-diameter (10 to 15 mm.) collection tubes and a solid coagulant (heparin or a mixture of ammonium and potassium oxalates) are used. With both estimations the need to transfer the samples of blood to a calibrated haematocrit tube is eliminated, the values being read against a proportional volume chart which indicates as percentages the relative proportions of parts of a sample irrespective of its total volume. The E.S.R. is read at 30 min., after which the tubes are transferred to a suitable centrifuge. It is claimed that with this method, which has been used in testing more than 10,000 samples of blood, the time necessary for centrifugation is much reduced, and altogether the time taken to make the double estimation is cut by more than half. Comparison of the results on a quantitative basis with those obtained by conventional methods showed that the method gives approximately equivalent values and is sufficiently accurate for routine clinical use.

A. Brown.

Hemagglutination Test in Rheumatoid Arthritis. I. Use of Red Cell Pattern as Endpoint in the Methods. BOISVER, P. L., BROCKETT, J. B., and DE FOREST, G. K. (1956). *Yale J. Biol. Med.*, **28**, 622. 1 fig., 5 refs.

Serum Cholinesterase Activity in Rheumatic Diseases. (L'attivita' colinesterasica del siero nelle malattie reumatiche.) CERVINI, C., and CIOCCI, A. (1956). *Rass. Fisiopat. clin. ter.*, **28**, 235. 2 figs, bibl.

Rheumatic Diseases and the Antistreptolysin-O Titre of the Serum. (Malattie reumatiche e titolo serico di antistreptolisine-O.) DANEO, V., MARAZZI, G., and SECONDO, G. (1956). *Reumatismo*, **8**, 82. Bibl.

Use of Anti-Rh Sera for demonstrating Agglutination Activating Factor in Rheumatoid Arthritis. WALLER, M. V., and VAUGHAN, J. H. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 198. 10 refs.

Study of the Agglutination Reaction with Erythrocytes sensitized with an Immune Serum in Chronic Inflammatory Rheumatism. (Etude de la réaction d'agglutination des globules rouges, sensibilisés par un immunsérum, au cours des rhumatismes inflammatoires chroniques.) EYQUEM, A., JACQUELINE, F., and JOCHEM, E. (1956). *Ann. Inst. Pasteur*, **90**, 697. 8 refs.

Behaviour of the Waaler-Rose Reaction in Fluid from Rheumatic Joints. (Ricerche sul comportamento della reazione di Waaler-Rose nei versamenti articolari di reumatici.) EINAUDI, G. (1956). *Reumatismo*, **8**, 98. 9 refs.

Studies on the Waaler-Rose Haemagglutination Test. I. Forssman's Antibody and Normal Anti-sheep (or Anti-Goat) Agglutinin in Human Serum. [In English.] SHICHIKAWA, K., ASANO, N., ORIHARA, M., MAYEDA, A., TAMATANI, Y., and YASUDA, J. (1956). *Acta rheum. scand.*, **2**, 34. 31 refs.

II. So-called AAF. [In English.] SHICHIKAWA, K., ASANO, N., ORIHARA, M., MAYEDA, A., TAMATANI, Y., and YASUDA, J. (1956). *Acta rheum. scand.*, **2**, 45. 31 refs.

III. AAF and Anti-Complementary Activities. [In English.] SHICHIKAWA, K., ASANO, N., ORIHARA, M., MAYEDA, A., TAMATANI, Y., and YASUDA, J. (1956). *Acta rheum. scand.*, **2**, 55. 31 refs.

ACTH, Cortisone, and Other Steroids

Effects of Prolonged Cortisone Therapy on the Statural Growth, Skeletal Maturation, and Metabolic Status of Children. BLODGETT, F. M., BURGIN, L., IEZZONI, D., GRIBETZ, D., and TALBOT, N. B. (1956). *New Engl. J. Med.*, **254**, 636. 6 figs, 5 refs.

The effect of prolonged administration of cortisone on the growth pattern in 36 children was studied at Massachusetts General Hospital, Boston. The children were suffering from adrenocortical virilism eleven, hypopituitarism eight, Addison's disease two, and allergy twenty, and were observed at intervals of 1 to 12 weeks. At each visit height and weight were recorded, a standard method of measurement being used, and radiographs were taken of the hands and wrists. Periodically electrocardiograms were obtained and the blood electrolyte concentration and urinary excretion of 17-ketosteroids determined.

Cortisone was given by mouth two or three times daily in a dosage varying from 4 to 60 mg. per square metre of body surface area per day, and within a few weeks of the start of treatment suppression of growth was observed. The dose causing growth suppression was 4 to 20 mg. per square metre of body surface per day in patients suffering from hypopituitarism, but in those with adrenocortical virilism a dosage of 30 to 50 mg. was necessary to cause reduction in growth of 20 to 70 per cent. Patients with allergic disorders were in normal endocrine balance, and a dose of 60 mg. was needed for a reduction in growth rate of 20 to 100 per cent. A compensatory growth spurt occurred in all patients except those with hypopituitarism when the dosage of cortisone was reduced. The authors tentatively conclude that the drug can be given for prolonged periods to growing children without necessarily altering the potential ultimate stature.

R. M. Todd.

Influence of Cortisone upon Protein Metabolism. CANNON, P. R., FRAZIER, L. E., and HUGHES, R. H. (1956). *A.M.A. Arch. Path.*, **61**, 271. 3 figs, 18 refs.

In experiments carried out at the University of Chicago the authors endeavoured to determine whether the inhibitory action of cortisone on over-all protein synthesis in the intact rat was primarily catabolic or anti-anabolic, and whether this action could be counteracted by increasing the calorie intake or by administering B vitamins or ascorbic acid. It was shown first, that with a diet deficient in protein, the values for weight loss and nitrogen and potassium excretion were higher in cortisone-treated than in untreated animals. Secondly, it was demonstrated that cortisone interfered with the restoration of weight which usually occurred when a high-protein diet was given to protein-depleted animals. This action of cortisone was not affected by potassium restriction, potassium supplements, or sodium supplements, and was associated with a slight negative balance of nitrogen and potassium. Moreover, it was unaffected by administration of rations reinforced with cyanocobalamin (vitamin B_{12}), ascorbic acid, or triple the amount of the vitamin mixture normally incorporated in the standard ration. However, an increase in the calorie intake, whether in the form of extra protein, carbohydrate, or fat, did cause an increase in weight, but carcase analyses revealed that this was mainly due to fat.

Using the term catabolism in a general sense the authors conclude that in these experiments cortisone "acted catabolically".

[The dose of cortisone acetate (3 to 5 mg. per rat per day by mouth or 2·5 to 5 mg. per rat per day by subcutaneous injection) was high.] *Denis Abelson.*

Recent Clinical and Laboratory Observations on the Treatment of Rheumatic Diseases with Prednisone, with Special Reference to Long-Term Treatment. (Ulteriori osservazioni cliniche e di laboratorio sulla cura delle malattie reumatiche con prednisone, con partisolare riguardo alle cure protratte.) ROBECCHI, A., DANEO, V., and MARRAZZI, G. (1956). *Minerva med.* (*Torino*), **47**, 295. 1 fig.

At the Rheumatological Centre of the City of Turin 137 patients with various rheumatic diseases were treated with prednisone given by mouth for periods ranging from a few days to 8 months. The series included eleven patients with rheumatic fever, 53 with rheumatoid arthritis, four with ankylosing spondylitis, twelve with acute gouty arthritis, seventeen with osteo-arthritis, 36 with peri-arthritis of the shoulder, and four with miscellaneous disorders.

The treatment of the various groups is described in detail; it was usually combined with and followed by other known methods of treatment. For example, in rheumatic fever the best results were achieved by giving prednisone by mouth in doses up to 50 mg. daily for 4 weeks, followed by ACTH for a few days when the condition had been stabilized, and finally a course of salicylates.

In rheumatoid arthritis the average initial dosage of prednisone was 30 to 40 mg. daily. After satisfactory general improvement had been obtained this was reduced to 5 to 20 mg. daily, which was given for periods up to 8 months.

This treatment was accompanied by general and dietary measures and in some cases by intra-articular injections of hydrocortisone or gold therapy. It is stated that the rapid action of prednisone permits the somewhat delayed effects of gold treatment to act in the most favourable circumstances, while the gold helps to stabilize the excellent, but short-lived, effects of prednisone.

Side-effects were rare and were not severe: irritability, sleeplessness, roundness of the face, and indigestion were the most frequently observed.

V. C. Medvei.

Pathophysiology and Treatment of Adrenal Crisis. LIPSETT, M. B., and PEARSON, O. H. (1956). *New Engl. J. Med.*, **254**, 511. 3 figs, 24 refs.

The clinical condition of adrenal crisis, as seen in bilaterally adrenalectomized patients deprived of cortisone, can be divided into two distinct syndromes: that of sodium loss and that due to deficiency of 17-hydroxycorticosteroids. Previously, sodium depletion was thought to be pre-eminent in patients with Addison's disease, and the usual treatment was with salt and deoxycortone acetate (DCA), although it was recognized that patients could die in adrenal crises even though sodium balance was maintained and serum electrolyte values were normal. Since bilateral adrenalectomy has been undertaken in human subjects the need for cortisone to maintain life has been recognized; this is in contrast to what obtains in adrenalectomized laboratory animals, which can be kept in reasonably good health with salt or DCA administration only. In many cases of adrenal insufficiency or of subtotal adrenalectomy the patient remains in good health without cortisone treatment; it is only when adrenal tissue is completely destroyed that the dependence on 17-hydroxycorticosteroids becomes apparent.

The authors, from the Sloan-Kettering Institute for Cancer Research and Memorial Center for Cancer and Allied Diseases, New York, present two studies of sodium balance in adrenalectomized patients from whom cortisone treatment had been withdrawn. Adequate sodium intake was ensured and positive sodium balance was maintained throughout the period of cortisone withdrawal, but the clinical condition of the patients deteriorated, and within 3 or 4 days adrenal crisis began to develop. Administration of cortisone quickly reversed the clinical picture. *Nancy Gough.*

Cushing's Syndrome and its Response to Adrenalectomy. [In English.] SKANSE, B., GYDELL, K., WULFF, H. B., and KOCH, F. (1956). *Acta med. scand.*, **154**, 119. 2 figs, 24 refs.

Subtotal adrenalectomy was carried out at the General Hospital, Malmö, Sweden, in seven patients (two men and five women) with Cushing's syndrome. The surgical technique is discussed, the authors expressing their preference for the retroperitoneal approach, although this

does not permit both glands to be exposed at once. They advise total resection on one side and a subtotal resection on the other, since this limits the extent of subsequent operation in the event of recurrence. In one of the cases in the series subtotal adrenalectomy was followed by partial remission; later, total adrenalectomy had to be performed for a relapse. One patient died from wound sepsis and renal failure. The authors emphasize that administration of cortisone before and after operation has lessened the risks of surgical treatment. In the remaining five patients there was complete remission, symptoms abating over periods of 6 months to one year or longer. In four cases microscopical examination revealed normal adrenal tissue. The mental state of the patients improved markedly after operation. In one case diabetes cleared up after adrenalectomy and in another, in which growth had been inhibited, there was an increase in height within less than 12 months. The eosinophil count and the urinary excretion of 11-oxycorticosteroids were the most informative laboratory determinations. *G. S. Crockett.*

Treatment of Nephrosis with Prednisolone. ARNEIL, G. C. (1956). *Lancet*, **1**, 409. 2 figs, 9 refs.

Hitherto the various methods of treating nephrosis, such as with cation-exchange resins, artificial infection with malaria, and hormones, have proved of limited value, all of them provoking diuresis on occasion, but failing to reduce the albuminuria consistently. The author, at the Royal Hospital for Sick Children, Glasgow, has therefore tried the effect of prednisolone in four cases of nephrosis in all of which the history, clinical findings, and biochemistry were typical. The patients were between 2½ and 8½ years old, and all were oedematous. The drug was given in doses up to 60 mg. per day.

In all four cases the albuminuria decreased strikingly within 6 days of starting treatment, and within 2 weeks the daily loss of albumin had decreased from 1 to 4 g. to less than 0·25 g. per 100 ml. Albuminuria ceased altogether in three cases, but reappeared in one of them 6 weeks after treatment was stopped. In all four cases diuresis began within 8 days of starting treatment and lasted from 6 to 8 days, the fluid lost amounting to 26 to 31 per cent. of (non-oedematous) body weight. An increase in serum albumin and γ-globulin levels occurred, and there was a return to normal of blood cholesterol concentration and erythrocyte sedimentation rate.

G. A. Smart.

Prolonged Discontinuous Treatment of the Nephrotic Syndrome in Children with ACTH and Cortisone. (Le traitement discontinu prolongé du syndrome néphrotique de l'enfant par l'ACTH et la cortisone.) DEBRÉ, R., ROYER, P., LEVEQUE, B., and MINOR, Z. (1956). *Sem. Hôp. Paris*, **32**, 263. 11 figs, 12 refs.

The authors have treated ten children with the nephrotic syndrome at the Clinique Médicale des Enfants, Paris, by giving large doses of ACTH or cortisone intermittently over a long period of time. The results were excellent, although the series was not large enough to prove the superiority of this over other types of hormone therapy. Treatment was divided into three periods:

(1) a period of 10 days during which ACTH was given in doses of 100 mg. a day;
(2) then 100 mg. ACTH or 300 mg. cortisone was given 4 days a week until a remission was obtained—if this had not occurred by the end of one month the doses were increased;
(3) a maintenance period with similar doses of ACTH or cortisone for 3 days a week for a total of 6 to 12 months.

G. A. Smart.

Use of Prednisone in the Management of Some Haemorrhagic States. STEFANINI, M., and MARTINO, N. B. (1956). *New Engl. J. Med.*, **254**, 313. 4 figs, 19 refs.

Because cortisone in large doses often causes unpleasant side-effects, prednisone in a dosage of 0·8 to 1·6 mg. per kg. body weight has been tried at Saint Elizabeth's Hospital, Boston, in the treatment of some haemorrhagic states. In six cases of primary thrombocytopenic purpura the haemorrhagic phenomena were well controlled, although the effect on the platelet count was variable and possibly less good than that of cortisone. Prednisone also controlled haemorrhage in the secondary thrombocytopenia of acute leukaemia (four cases). In two patients with aplastic anaemia there was partial control of bleeding but no reduction in the need for blood transfusion. An apparent remission was obtained in two cases of acute anaphylactoid purpura, but there was no effect in one chronic case. The most striking results were observed in seven patients with "vascular pseudohaemophilia" (von Willebrand's disease), in whom the bleeding time was reduced. In spite of the large doses employed, side-effects of the drug were slight and in no case necessitated cessation of treatment. *P. C. Reynell.*

Subacute Non-Suppurative Thyroiditis. Treatment with Cortisone and Corticotrophin. IZAK, G., and STEIN, Y. (1956). *Lancet*, **1**, 225. 12 refs.

In this paper from the Rothschild Hadassah-University Hospital, Jerusalem, five cases of subacute non-suppurative thyroiditis treated with either corticotrophin or cortisone are reported. In all cases the condition was diagnosed clinically. The patients, females aged 35 to 64, complained of sharp pain at the lower anterior region of the neck which was aggravated by swallowing. There had been intermittent pyrexia for 2 to 6 weeks before admission. On physical examination all the patients appeared seriously ill and were apprehensive and sweating profusely; the pulse rate was high. A fine tremor of the fingers was observed and in all cases there was a diffuse moderate enlargement of the thyroid, which was exquisitely tender and firm. The erythrocyte sedimentation rate was increased and there was leucocytosis. The basal metabolic rate was raised in all cases but the uptake of radioactive iodine was decreased. Within 24 hours of administration of cortisone or corticotrophin a dramatic response was observed, temperature became normal, pain subsided, and the general condition

improved considerably. Treatment was continued, the dosage being decreased, for 4 weeks. No immediate or late relapses were observed in the three patients treated with cortisone; in two given corticotrophin there were mild relapses, which were controlled by an increased dose of the drug. No late recurrences were observed and none of the patients subsequently developed myxoedema. *G. A. Smart.*

Acute Renal Effects of 9-Alpha-Fluoro Hydrocortisone in Human Subjects with Infant Adrenals. HUFFMAN, E. R., WILSON, G. M., CLARK, G. M., and SMYTH, C. J. (1956). *J. Lab. clin. Med.*, **47**, 747. 13 refs.

Changes in the Indications for Cortisone Treatment. (Evolution dans les indications thérapeutiques de la Cortisone.) BICKEL, G. (1956). *Bull. schweiz. Akad. med. Wiss.*, **12**, 144.

Experience with Hydrocortisone in the Local Treatment of Articular Rheumatism. (Erfahrungen mit Hydrocortison in der lokalen Behandlung des Gelenkrheumatismus.) BEIGLBÖCK, W., and BRUMMUND, W. (1956). *Dtsch. med. Wschr.*, **81**, 1195. Bibl.

Use of High Doses of Hydrocortisone Acetate in the Local Treatment of Joint Disease. (Sull'impiego di dosi elevate di idrocortisone acetato nel trattamento locale delle artropatie.) ROBECCHI, A., CARTESEGNA, F., and DANEO, V. (1956). *Reumatismo*, **8**, 214.

Continuous Corticotherapy in Chronic Inflammatory Rheumatism. (La corticothérapie continue dans les rhumatismes inflammatoires croniques.) ARLET, J., and MOLE, J. (1956). *Rev. esp. Reum.*, **6**, 363. 29 refs.

Evaluation of a New Liquid Dosage Form of Hydrocortisone. KELLEY, V. C., DONE, A. K., AINGER, L. E., ELY, R. S., FORIST, A. A., and COLLINS, E. J. (1956). *J. Pediat.*, **49**, 26. 2 figs, 5 refs.

Corticotropins in the Treatment of Transient Synovitis of the Hip in Children. ROTHSCHILD, H. B., RUSS, J. D., and WASSERMAN, C. F. (1956). *J. Pediat.*, **49**, 33. 9 refs.

Intra-Articular Hydrocortisone. (Hidrocortisona intra-articular.) LEAL, J. P., and FERNÁNDEZ, DEL VALLADO P. (1956). *Rev. clín. esp.*, **61**, 149. 21 refs.

Therapeutic Effect of Intra-Articular Injections of Prednisone and Prednisolone. (Recherches et observations sur l'effet thérapeutique des injections intra-articulaires de prednisone et de prednisolone.) ROBECCHI, A., CARTESEGNA, F., and DANEO, V. (1956). *Rev. Rhum.*, **23**, 218.

Treatment of Chronic Articular Rheumatism with "Deltacortril" (Prednisolone). (Behandlung des chronischen Gelenkrheumatismus mit Deltacortril (Prednisolon).) GOLZ, G. (1956). *Medizinische*, **20**, 766. 9 refs.

Treatment of Rheumatic Diseases with Prednisone in Association with Acetylsalicylic Acid. (Terapia delle malattie reumatiche con prednisone associato ad acido acetil-salicilico.) ROBECCHI, A., DANEO, V., and MARRAZZI, G. (1956). *Reumatismo*, **8**, 121. 11 refs.

Other General Subjects

Myelofibrosis and Osteomyelosclerosis. The Osteomyeloreticulosis Syndrome. (Myelofibrose und Osteomyelosklerose. (Osteomyeloretikulose-Syndrom.).) ROHR, K. (1956). *Acta haemat.* (*Basel*), **15**, 209. 11 figs, 50 refs.

The syndrome of myelofibrosis is characterized by splenomegaly, the presence of immature cells, striking poikilocytosis, and giant platelets in the peripheral blood, and fibrosclerosis of the bone marrow, often with osteosclerosis, and is usually associated with extramedullary haematopoiesis in the spleen, liver, and lymph nodes. The present author discusses a series of twenty cases conforming to this definition, twelve of which were examined post mortem at the Zurich Pathological Institute, while biopsy specimens of the bone marrow were examined in four others. The sex distribution was equal, the patients' ages ranged from 40 to 70 years, and the duration of the illness from 1 to 14 years. In some cases the spleen was already huge at the time advice was first sought, and in these the course was short. The three cases with the longest survival presented with polycythaemia 10 to 15 years before the final phase of the illness. In seven of the author's cases the blood picture was leukaemoid, while in three cases the disease was of a neoplastic character, one resembling Hodgkin's disease, one showing granulomatous foci in the head of the femur and in the serous membranes, and one having an enormous tumour originating in the mesenteric lymph nodes, the histological examination of which showed intense fibrous-tissue proliferation with reticulin and collagen fibrils, giant cells, and numerous blast cells. In eight cases febrile episodes occurred which responded to cortisone but not to antibiotics. Cirrhosis of the liver was found in five cases. Splenectomy was performed on four patients, who survived 3 months, 9 months, 2 years, and 4 years respectively.

The pathogenesis of myelofibrosis is discussed in relation to the theories currently prevailing. The author considers it to be an irreversible, progressive, proliferative condition with a tendency to cellular dedifferentiation and would place it among the neoplastic reticuloses. He suggests that the term "osteomyeloreticulosis" is more suitable than myelofibrosis, since the condition originates in the reticulo-histiocytic system of myelopoietic organs. Its development may be attributable to a tumour *anlage*—possibly due to genetic or to viral factors acting in early embryonic life. Later on, a precipitating "realization factor" may exert a contributory effect. *F. Hillman.*

Physiology of Human Cartilage. (К Физиологии хрящевой ткани человека.) VINOGRADOVA, T. P. (1956). *Arkh. Patol.*, **18**, 24, No. 2. 7 figs, 19 refs.

In this description of a histological study of normal and dystrophic human cartilage carried out at the

Institute of Traumatology and Orthopaedics, Moscow, the author reports that cartilage grows in a twofold manner: (1) by apposition, and (2) by increase of interstitial tissue. Growth by apposition implies transformation of the perichondrium and other contiguous tissue into cartilage. In regard to interstitial growth the author observes that even the most differentiated cells in the cartilage do not lose their proliferative ability. In certain forms of dystrophy a chondro-mucoid substance can be seen to penetrate into the surrounding tissue and veins. It is pointed out that "asbestization" of the matrix is not a mere unmasking of pre-existing collagen fibres, but actually the new formation of such fibres.

L. Crome

Reversal of Pulmonary Hypertrophic Osteo-Arthropathy by Vagotomy. FLAVELL, G. (1956). *Lancet*, **1**, 260. 6 refs.

Hypertrophic osteo-arthropathy is found most typically as a secondary manifestation of a chronic pulmonary or cardiac disorder. It is extremely rare in chronic pulmonary tuberculosis, yet its association with bronchial carcinoma is well recognized. Indeed, a patient may be treated for as long as 12 months for "rheumatism" or "arthritis" before a neoplasm is revealed by radiography. In the experience of the present author joint pain occurs in 5 to 10 per cent. of cases of bronchial carcinoma, and careful inquiry usually shows that it was the first symptom to be noted.

It has long been known that resection of the growth is followed instantly by the cessation of all joint pain and the resolution of secondary changes in the nails, but no satisfactory explanation of the mechanism involved has been put forward. The author, in the belief that only the interruption of a neural reflex originating in the affected lung could explain the abrupt and consistent cessation of pain, has observed the effect on hypertrophic osteo-arthropathy in a number of patients with inoperable bronchial carcinoma of:

(1) performing as complete a hilar clearance as possible on the affected side, dividing the pleural investment and all fibres of the vagus and sympathetic nerves entering the root of the lung; and

(2) isolating and dividing the vagus branches to the affected lung, avoiding all interference with the rest of the hilum.

Reports of five cases are given, two treated by the first and three by the second method. The effect was equally dramatic in all cases, with immediate and complete relief of joint symptoms, and resolution of joint effusions within a few days. Exploratory thoracotomy alone in two patients with clubbing and arthralgia had no effect.

D. P. McDonald.

Unusual Hyperkinesia in Cerebral Rheumatism. (Своеобразные гиперкинезы при ревматических заболеваниях головного мозга) SLONIMSKAYA, V. M., and BOBROVSKAYA, G. D. (1955). *Zh. Nevropat. Psikhiat.*, **55**, 585. 10 refs.

Rheumatism is generally thought to be of an allergic nature, manifesting itself mainly in mesenchymal tissues, but often involving also the parenchyma. Some forms, however, affect the central nervous system, although their rheumatic origin is not always recognized. According to the authors, radiculitis and neuritis of rheumatic origin have long been known, as have also chorea and cerebral embolism. Less often recognized are forms of encephalitis, torsional dystonia, paroxysms of motor spasm (both tonic and clonic), and athetotic movements associated with a rheumatic carditis or other evidence of rheumatism. In this paper five cases are described in detail to illustrate these forms. The authors emphasize that torsional dystonia, generally regarded as a degenerative condition, may result from an exogenous infective process such as rheumatism. In all the cases decribed there was a history of repeated quinsies, mastoiditis, scarlet fever, or chorea which had responded to a greater or lesser extent to antirheumatic treatment.

L. Firman-Edwards.

INDEX TO VOLUME XV, 1956

* indicates that only the title of the article is given

ABD EL WAHAB, E. M., 82
Abdomen, acute, and lupus erythematosus, *409
ABRAMS, N. R., 395
Acid, glucuronic, 357
——, hyaluronic, in arthritis, rheumatoid, 357
——, ——, biosynthesis of, by group-A streptococci, 378
——, ——, isolated from synovial fluid by electroconvection, 67
——, sialic, test for inflammation, 387
——, uric, in gout, 61
——, ——, in serum, 268, *409
ACKER, M., 399
ACTH in anaemia of arthritis, rheumatoid, 12
—— in arthritis, rheumatoid, 12, 410
——, acquired resistance to, 124
——, clinical and biochemical findings during therapy, 411
——, factors influencing response to, 411
—— in rheumatism, acute, 366
——, stress during therapy, effects of, 410
Acute rheumatism: *see* Rheumatism, acute
Adrenalectomy and arthritis, rheumatoid, *78
Adrenocortical function, cortisone and, 396
Agglutination, anti-Rh antibody in, *410
—— factor in arthritis, rheumatoid, 382
—— inhibitor system, 76
—— test in arthritis, rheumatoid, 74 *bis*, *410 *bis*
—— —— with human serum, 246
—— ——, mineral acid in, *408
—— —— in rheumatism, acute, 365
—— —— and serum euglobulin polysaccharides in arthritis, rheumatoid, 74
—— titres in spondylitis, ankylosing, 41
AHERN, ARCH M.: *see* ZUCKER, JACK, etc., 238
AITCHISON, J. D., and WYNN WILLIAMS, A.: Pulmonary changes in disseminated lupus erythematosus, 26
ALEXANDER, R., 266
ALEXANDER, W. R. M., RICHMOND, J., ROY, L. M. H., and DUTHIE, J. J. R.: Nature of anaemia in rheumatoid arthritis. II. Survival of transfused erythrocytes in patients with rheumatoid arthritis, 12
*ALLEGRETTI, J. E., 408
Allergy to ACTH, 124
Amyloidosis in arthritis, rheumatoid, *409
——, familial, *409
AMERICAN RHEUMATISM ASSOCIATION: Second Interim Scientific Session, December, 1955, 61
—— —— ——: Annual meeting, June 8 and 9, 1956, 266
—— —— ——: Proceedings of the Annual Meeting, 1956, 374
—— —— ——: Presidential Address, 374
Amidopyrin in rheumatism, acute, 366
Anaemia, ACTH and, 12
—— in arthritis, rheumatoid, 12, 151, 217
——, intravenous iron and, 17
ANGEVINE, D. M., 378, 381, 408, *408
Ankylosis, spinal, in adults after juvenile rheumatoid arthritis, 42
Ankylosing spondylitis: *see* Spondylitis, ankylosing
ANSELL, B., 263
—— and BYWATERS, E. G. L.: Growth in Still's disease, 295
Antibiotics in rheumatism, acute, 366
Antibody response to tissue antigens in rheumatism, acute, 364
Anti-Rh antibody and agglutination test, *410
Antistreptolysin-O titres, 269
Aortitis in arthritis, rheumatoid, *409
ARDEN, G. P.: Comparison of cortisone acetate and a codeine mixture as adjuvant treatment in judet arthroplasty, 173
Arteritis, renal, in scleroderma, *409
Artery, pulmonary, in lupus erythematosus, 28
Arthritis, disability evaluation in, *409 *bis*
—— and gout, 264
——, hand corset for, 346
—— of hip joint, arthroplasty in, 72
——, mechanics of joint function in, 265
—— and psoriasis, 348
Arthritis, rehabilitation in, 399
—— and Rheumatism Foundation, East Pennsylvania Chapter, 412
——, erosive, and psoriasis, 349
——, experimental, 379
——, familial, 349
——, gouty, 233, 406 *bis*
——, ——, colchicine in, *410
——, ——, synovial biopsy in diagnosis of, *409
——, iatrogenic, *78
——, infectious, 271
——, juvenile, followed by adult spondylitis, 40
——, rheumatoid, ACTH in, 124, 410 *bis*
——, ——, adrenalectomy and, *78
——, ——, agglutination test in, 74 *bis*
——, ——, amyloidosis in, *409
——, ——, anaemia in, 12, 217
——, ——, aortitis in, *409
——, ——, aspirin in, 385
——, ——, capillary fragility in, *409
——, ——, in children: *see* Still's disease
——, ——, chloroquine in, 251, *409
——, ——, clinical and biochemical findings in, during steroid therapy, 411
——, ——, Δ^{1}-9-α-fluoro hydrocortisone acetate in, 237
——, ——, diagnosis of, 7, 401
——, ——, electrophoresis in, 387, *409
——, ——, evaluation of, *78, 134, 254
——, ——, gold in, 394
——, ——, Hargraves cell and, *409
——, ——, hyaluronic acid in, 357
——, ——, hydrocortisone in, 134, 340
——, ——, hydrocortisone *ter*-butyl acetate in, 258
——, ——, incidence of in population sample, 1
——, ——, iron therapy of, 17, 51
——, ——, and kerato-conjunctivitis sicca, 21
——, ——, latex-fixation test in, 384
——, ——, L.E. phenomenon in, 211, *409
——, ——, and pericarditis, 176
——, ——, phenylbutazone in, *409
——, ——, plasma corticoid studies in, *79, 392
——, ——, prednisone in, *78, *409 *bis*
——, ——, procaine in, 134
——, ——, prognosis of, 263
——, ——, psychology of, 272
——, ——, psychosomatic study of children with, 398
——, ——, quantitation of activity of, 393
——, ——, radiology of, observer differences in, 55
——, ——, serology of, 266 *bis*, 381, 382, 383, 384
——, ——, serum agglutinating factor in, 382
——, ——, specific serum factor, 270
——, ——, in swine, 62
——, ——, in twins, *409
——, ——, urinary excretion of 17-hydroxycorticoids and 17-keto-steroids in, 69
——, ——, and uveitis, 144
Arthroplasty of hip joint, 72
——, Judet, 173
Aspirin, metabolic effects of, 385
Atebrin: *see* Chloroquine
*AUERBACH, V. H., 78
AUSTRALIAN RHEUMATISM COUNCIL, Report for 1954-1955, 191
Auto-antibody formation in rheumatism, acute, 366
Auto-immune antibodies to heart tissue in rabbits inoculated with streptococci, 386

BACHMAN, D., 385, 392
*BAEDER, D. H., 78
BAGNALL, A. W., 403, *408, *410
BAKER, L. A., 400
BALLABIO, C. B.: *see* VILLA, L., etc., 237

*Banowitch, M., 410
Barber, H. Stuart: *see* Millard, J. B., etc., 51
Barr, J. H., Jr., 397, *409
Bartels, E. C., 406
Barthold, E. A., 396
Barton, E. M., 400
*Bartter, F. C., 409
Bated, R. C., 387
Batterman, R. C., 395, *409
Bauer, W., 379, 385
Bayles, T. B., 73, 394
Beadenkopf, W. G., 389
Benadryl in gout, 234
Benemid in gout, 406
Bennett, G. A., 401
Bergenstal, D. M., 78, *78
*Berry, D., 409
Beta-aminopropionitrile (BAPN) and connective tissue, 378
—— —— —— —— alterations in rats, *408
Bier, Frida: *see* Kellgren, J. H., etc., 55
Biopsy, synovial, in diagnosis of gout, *409
*Black, A., 409
Black, R. L., 73, 76, 398, *409
Blair, J. R., 380
Blom, G. E., 398
Blood, peripheral, in arthritis, rheumatoid, 221
—— transfusion in arthritis, rheumatoid, from normal and rheumatic donors, 12
—— volume, 153
Boisvert, P. L., 74
Bone defects in Still's disease, 300
—— density, measurement of, 115
—— disease, metabolic, 270
—— erosion, radiology of, 55
—— marrow biopsy and histology, 219
—— —— changes and anaemia, 217
Book Reviews:
Benedek, Tibor: Rheumatoid Arthritis and Psoriasis Vulgaris, 1955, 180
Castro Paullier, Victor M.: Artritis reumatoidea, 1955, 80
Coburn, A. F., Morre, L. V., Wood, J., and Roberts, M.: Splenin A in Rheumatic Fever, 1955, 80
Coste, F., and Bourel, M.: Rhumatisme chronique. Méthodes thérapeutiques, 1956, 180
Cyriax, James: Textbook of Orthopaedic Medicine, Volume II: Treatment by Manipulation and Massage, 5th edition, 1955, 80
——: Hydrocortisone in Orthopaedic Medicine, 1956, 180
Empire Rheumatism Council: Osteo-Arthritis. A Handbook for Patients, 1956, 262
Forestier, J., Jacqueline, F., and Rotes-Querol, J.: Ankylosing Spondylitis, 1956, 261
Hackett, George Stuart: Joint Ligament Relaxation treated by Fibro-Osseous Proliferation, 1956, 373
Hopmann, R. (ed.): Der Rheumatismus, 1956, 373
Ravault, Pierre P., and Vignon, Georges: Rhumatologie Clinique, 1956, 261
Talbott, John H., and Moleres Ferrandis, R.: Collagen Diseases, 1956, 262
Bowie, M. A., 63
*Brain, Sir Russell, 263
Bronner, F., 68
*Bronsky, D., 409
Brooks, R. V., 411
Bunim, J. J., 62, 74, 76, 392, 393, 397, 398, *409
Butazolidin and pituitary-adrenal function in guinea-pigs, *78
Bywaters, E. G. L., 263
——: *see* Ansell, B. M., etc., 295
——: *see* Fearnley, G. R., etc., 134

Calkins, E., 69, 70, 385
Canada: Canadian Rheumatism Association (Société Canadienne de Rhumatologie) Annual Meeting, 1956, 267
Capener, Norman, 265
Capillary fragility in arthritis, rheumatoid, *409
Carditis and rheumatism, acute, 164, 166, 366
—— and spondylitis, 81
Cartilage, chrondroitin sulphate in, 68
—— mucoprotein and dye-diffusion, *78
Cecil, R. L., 395
Cell volume, 154
*Champlin, B., 409 *bis*
Children, arthritic, psychosomatic study of, 398
——, growth of, in Still's disease, 295
——, rheumatism, acute, in, 162
Chloroquine in arthritis, rheumatoid, 251, *409
—— in lupus erythematosus, 400
——, toxic effects of, 255
Chondroitin sulphate in cartilage, 68
Cifonelli, J. A., 378
Circulation, absorption of hydrocortisone in, 327
Clark, G. M., 75, *79
Clayton, B. E., 411
*Clemmons, J. J., 408
Cobb, S., 399, 401
Coburn, A. F., 387, 390
Codeine in Judet arthroplasty, 173
Colcemide in gout, 234, *410
Colchicine in gout, 234, 407, *410
Collagen changes, traumatic, 65
—— disease diagnosis by serum complement titres, 74
—— ——, fibrinoid and plasma cells in, 381
—— fibrils, electronmicroscopy of, 263
——, neutral salt-soluble, 82
Collagenase susceptibility, *78
Collodion agglutination, 371
*Colsky, J., 410
Congresses:
American Rheumatism Association, 61, 374
Australian Rheumatism Council, 191
Canadian Rheumatism Association, 267
Empire Rheumatism Association, 183
Heberden Society, 81, 189, 263, 410
Ist International Symposium on Rheumatic Fever, Mexico, 1956, 181
Ligue Internationale contre le Rhumatisme, 83, 267
Sociedad Española del Reumatismo, 188
Società Italiana di Reumatologia, 82, 182
Société Canadienne de Rhumatologie, 267
World Confederation of Physiotherapy, 83
Connective tissue, beta-aminopropionitrile and, 378, *408
—— —— changes, traumatic, experimental, 65
Contreras, Vincent: *see* Ziff, Morris, etc., 40, 227
Cook, E. R., 264
Corticosteroids, skin tests of, *78
Corticosterone metabolism, 391
Corticotrophin: *see* ACTH
Cortisone acetate and adrenocortical function, 396
——, hypersensitivity to, 270
—— in Judet arthroplasty, 173
—— in polyarteritis, 49
—— and renal arteritis in scleroderma, *409
—— in rheumatism, acute, 366
—— in Still's disease, 313
*Coventry, M. B., 408
*Craig, H. W., 408
Crain, D. C., Jr., 74
C-Reactive protein estimation, 339
Cytology of bone marrow, 223

Davis, P. S., 411
Deformity in arthritis, rheumatoid, quantitation of, 393
Delta[1] cortisone: *see* Prednisone
—— 9-α-fluoro hydrocortisone, 76, 237, 327
*Denko, C. W., 78, *409
Diagnosis of arthritis, rheumatoid, 7, 9
—— ——, ——, criteria for, 401
—— of collagen disease by serum complement fixation, 74
—— of gout by synovial biopsy, *409
—— of osteo-arthritis, 7
—— of spondylitis, ankylosing, 386
Diet in gout, 407
DiFerrante, N., 68
Dingle, J. T., 264
Disability evaluation in arthritis, *409 *bis*
DOCA in gout, 234
Done, A. K., 71
*Dordick, J. R., 409
Dorfman, A., 378
Doyle, L. P., 62
*Dresner, E., 78
Duff, I. F., 67
*Duffy, M. L., 409 *bis*
*Durrum, E. L., 409
*Duryee, A. W., 409
Duthie, J. J. R.: *see* Alexander, W. R. M., etc., 12
——: *see* Richmond, J., etc., 217
Dziewiatkowski, D., 68

Eadie, Stella: *see* Thompson, Malcolm, etc., 21
Egelius, N., Jonsson, E., and Sundblad, L.: Studies of hyaluronic acid in rheumatoid arthritis, 357
*Eisenbeis, C. H., Jr., 409
"Elastin", electronmicroscopy of, 263
Electrocardiogram in lupus erythematosus, 27

Electroconvection of hyaluronic acid from synovial fluid, 67
Electronmicroscopy of transformation of collagen fibrils into "elastin", 263
Electrophoresis, 269
—— in arthritis, rheumatoid, *409
—— of serum polysaccharides, 387
ELY, R. S., 391
EMPIRE RHEUMATISM COUNCIL:
Exhibition, Royal Society of Health, 1956, 83
19th Annual Report, 1955, 183
ENGLEMAN, E. P., 396
Enzymatic adaptation in animals, *78
Epidemiology of rheumatism, acute, 390
EPSTEIN, W., 383
Erysipelothrix rhusiopathiae in swine, 63
Erythrocyte sedimentation estimation, 339
—— —— rate in arthritis, rheumatoid, 52
—— —— —— and haemoglobin, 214
—— —— —— and plasma volume, 156
Erythrocytes, transfused, survival of in arthritis, rheumatoid, 12
ESSERMAN, P., 400
*EVANS, SIR HORACE, 263
EVANS, R. L., 76

*FAIRBANKS, R., 410
*FALLET, G., 410
Familial incidence of arthritis, 349
—— —— —— psoriasis, 349
FEARNLEY, G. R., LACKNER, RITA, MEANOCK, R. I., and BYWATERS, E. G. L.: Pilot study of intra-articular procaine and hydrocortisone acetate in rheumatoid arthritis, 134
FEICHTMEIR, T. V., 396
*FELDHAKE, C., 409
FELDMAN, H. A., 389
Ferrivenin, 51
Fibrinogen, 339
——, heparin-precipitable fraction of, 66
Fibrinoid in collagen disease, 381
—— in rheumatoid nodules, 268
"Fibrositis" and joint disease, *409
FOREST, G. K. DE, 74
*FOSKE, R. M., 409
FOXWORTHY, D. T., 400
Fractures in rats injected with beta-aminopropionitrile, *408
FREEDMAN, A.: Chloroquine and rheumatoid arthritis. A short-term controlled trial, 251
FREMONT-SMITH, P., 394
FREYBERG, R. H., 396
*FRIEDMAN, I. A., 409
Frostbite, vascular and articular lesions of, 380

GARDNER, D. L.: *see* RICHMOND, J., etc., 217
Gastric secretion, steroid therapy and, 397
GIBSON, H. J., and LING, N. R.: Modified Waaler-Rose reaction employing sensitized human cells, 246
GILLILAND, I., 82
Glove, as splint for arthritic hand, 346
GLYN, J. H.: Laboratory aids in steroid therapy, 338
——, *263, 266
Gold, radio-active, animal experiments with, 264
—— therapy, "sensitivity" produced by, 394
——, urinary excretion of, *409
*GOLDMAN, L., 78
*GOOD, T. A., 78
GOSLINGS, J.: *see* KIEVITS, J. H., etc., 211
Gout and arthritis, 264
——, Benadryl in, 234
——, colcemide in, 234, *410
——, colchicine in, 233, *410
—— and concurrent disorders, *409
——, diagnosis of, by synovial biopsy, *409
——, DOCA in, 234
——, kidney lesions in, 61
——, panel discussion on, 403
—— and psoriasis, 354
——, purine biosynthesis and, 404
——, uric acid formation in, 61
——, 17-ketosteroid excretion in, 264
Granuloma pouch and remote inflammation, *79
GROSS, J., 302, 377
*GROSSMAN, A. J., 409
Growth hormone and S^{35} fixation in stomach of hypophysectomized rats, *409
—— in Still's disease, 295
GUTMAN, A., 403, *410

Haemodilution in rheumatoid disease, 151
Haemoglobin and erythrocyte sedimentation rate, 214
—— estimation, 155
—— values in arthritis, rheumatoid, 52
Hand, arthritic, corset for, 346
——, radiographs of, in diagnosis of arthritis, 55
Hargraves cell phenomenon in arthritis, rheumatoid, *409
*HARSHA, W. N., 409
HATCHER, C. H., 408
Heart disease, auto-immune bodies in, 386
—— —— and tendonitis, *409
Heberden Round, Bath, 1956, 263
HEBERDEN SOCIETY:
Clinical meeting, November 26, 1955, 81
Annual report, 1955, 189
Clinical meeting, February 24, 1956, 263
Clinical meeting, October 19, 1956, 410
Height of children with Still's disease, 295
HELLBAUM, A. A., 393, *409
HENCH, P. S., 392
Heparin precipitation fraction of fibrinogen, 66
Heredity and amyloidosis, *409
*HERMANN, I. F., 409
HERSCHEL, H.: A hand corset, 346
HESS, E. L., 387, 388
Hexosamine estimation, 339, 343
HIBBETT, L. L., 69
High purity Acthar gel: *see* ACTH
HIJMANS, W.: *see* KIEVITS, J. H., etc., 211
HILL, A. G. S., 265
HILL, S. R., JR., 69, 72
Hip, synovial cyst of, *408
—— joint, arthroplasty of, 72, 173
—— ——, hydrocortisone and procaine injection into, 330
—— ——, osteo-arthritis of, 330
—— ——, resection-angulation operation, *78
Histology of bone marrow, 222
Hitchens, R. A. N.: Decline of acute rheumatism, 160
Hodgkin's disease, 271
*HOENE, R., 79
HOLLANDER, JOSEPH L., and MOORE, ROBERT: Studies in osteo-arthritis using intra-articular temperature response to injection of hydrocortisone acetate and prednisone, 320
——, *78, 394
HOLLEY, H. L., 69, *78
Hormone therapy and growth in Still's disease, 313
Howell, R. S., 70
Hughes, E. R., 391
Hyaluronidase, 357
Hydrocortisone and erythrocyte sedimentation rate, 360
—— and gastric secretion, 397
—— and hyaluronic acid, 358
—— injected by needle, or Hypospray, *409
—— metabolism in joint cavity, *410
—— in osteo-arthritis, 327, 330
—— in painful shoulder (film), 270, *410
—— in plasma ,392
——, serology of, 340, 341
—— and synovial fluid viscosity, 360
—— and S^{35} fixation in stomach of hypophysectomized rats, *409
—— acetate, intra-articular, *408
—— ——, ——, injected by hypospray, 227
—— ——, ——, in osteo-arthritis, 320
—— ——, ——, and procaine in arthritis, rheumatoid, 134
—— *ter*-butyl acetate, intra-articular, 258
—— —— and hyaluronic acid, 358
Hyland, P. J., 387
Hyperlipaemia after injection of lipid mobilizer from cortisone-treated subjects, *78
Hypersensitivity to cortisone, 270
Hypospray jet injector for intra-articular hydrocortisone acetate, 227, *409

Imferon, 51
Immunology of heart tissue, 386
—— of rheumatism, acute, 364
Inflammation, test for, 387
Injection technique into hip-joint, 330
International League against Rheumatism: *see* Ligue Internationale contre le Rhumatisme
Iron in bone marrow, 217
——, intramuscular, in arthritis, rheumatoid, 51
——, intravenous, and anaemia of arthritis, rheumatoid, 17
——, ——, in arthritis, rheumatoid, 51
*IRVINE, J. H., 78, *409 *bis*
ISDALE, I., 82, 263
ISHMAEL, W. K., 388, *409 *bis*
*ISSELBACHER, J., 78

ITALY: Società Italiana di Reumatologia:
IV Rome Rheumatology day, 1956, 182
X Congress, Milan, 1956, 182
Third Acqui Prize, 1957, 82

JACKSON, D. S., 82
JACOX, R., 401
JAFFE, H., 399
Jaw involvement in Still's disease, 312
JEFFREY, M. R.: Haemodilution in rheumatoid disease, 151
——, 264
JENKINS, J., 76
JESSAR, R., 401
JOHNSON, A. M., 383
JOHNSON, L. C., 408
Joint cavity, absorption of hydrocortisone into, 327
—— disease and "fibrositis", *409
—— function, mechanics of, 265
—— erosion in arthritis, 349
—— —— in Still's disease, 300
——, osteo-arthritis in, 330
—— temperature in osteo-arthritis, 320
—— —— and vasodilatation and constriction of extremities, *78, 241
JONSSON, E.: *see* EGELIUS, N., etc., 357
Judet arthroplasty, 173

KAMMERER, W. H., 397
KANTOR, T. G., 66, *78
*KAPLAN, L., 409
KAPLAN, M. H., 386
*KARK, R. M., 409 *ter*
KEECH, M., 263
KELLEY, V. C., 70, 71, *78
KELLGREN, J. H., 81
—— and BIER, FRIDA: Radiological signs of rheumatoid arthritis, 55
—— and LAWRENCE, J. S.: Rheumatoid arthritis in a population sample, 1
Kerato-conjunctivitis sicca and arthritis, rheumatoid, 21
KERBY, G. P., 384, 388, *408
KERSLEY, G. D., 263
*KLEIN, R., 409
*KLINEFELTER, H., JR., 78
Knee, intra-articular temperature of, 241
—— joint, osteo-arthritis of, 322
——, prevention of deformity, 268
*KRON, K. M., 409
Kidney involvement in scleroderma, 73
—— lesions in gout, 61, 408
—— —— and lupus nephritis, *409
KIEVITS, J. H., GOSLINGS, J., SCHUIT, H. R. E., and HIJMANS, W.: Rheumatoid arthritis and the positive L.E.-cell phenomenon, 211
KUHNS, W. J., 387
KULKA, J. P., 380, 382, 408
*KUZELL, W. C., 409 *quater*

LACKNER, RITA: *see* FEARNLEY, G. R., etc., 134
LALIGH, J. J., 378
LANSBURY, J., *78, 393, 398
Lantern slides on pathology of arthritis and rheumatism (Demonstration and Discussion), *408
Presentation in Philadelphia, 412
*LARSON, E., 409
LARZELERE, R. G., 396
LASTER, L., 61
Latex-fixation test in arthritis, rheumatoid, 384
Lathyrus factor: *see* Beta-aminopropionitrile
LAWRENCE, J. S., 81
——: *see* KELLGREN, J. H., etc., 1
LEE, S. L., 73
LEFF, S.: Modern trends in rheumatism, acute, 33
*LEIFER, P., 409
Leigh, Lancs., arthritis in a population survey, 58
*LEINWAND, I., 409
Leukaemia, 271
LEVEAUX, V. M., and QUIN, C. E.: Local injection of hydrocortisone and procaine in osteo-arthritis of the hip joint, 330
LEVIN, MELVIN, H., MARCUS, STANLEY, STRANGE, DAVID, and SWEZEY, ROBERT L.: Therapeutic trials in acute gouty arthritis, 233
——, *409
LIGUE INTERNATIONALE CONTRE LE RHUMATISME:
IX International Congress, Toronto, 1957, 83, 267
LING, N. R.: *see* GIBSON, H. J., etc., 246
LONG, R. T., 398
LOSPALLUTO, J., 382, *410
LOVELL, R. R. H., and SCOTT, G. B. D.: Hypertrophic osteo-arthropathy in polyarteritis, 46
Low back pain, treatment of, *408
LUFT, A. P. A., 65
Lung disease and osteo-arthropathy, 46
—— lesions in lupus erythematosus, 26
Lupus erythematosus cell phenomenon and arthritis, rheumatoid, 211, *409
—— ——, chloroquine in, 400
—— ——, electrocardiograph in, 27
—— ——, pulmonary changes in, 26
—— ——, systemic, and acute abdomen, *409
—— ——, ——, macroscopic test for, 73
—— ——, ——, and pregnancy, *409
—— ——, ——, steroid therapy in, 400
—— nephritis and renal lesions, *409

*MCCLENDON, R., 78, *409
*MCCOY, F. W., 78
MCEWEN, C., 389, 390, 400, 408, *410 *bis*
——: *see* ZIFF, MORRIS, etc., 40
MACHEK, OTAKAR: *see* ZUCKNER, JACK, etc., 258
MACNAIR, M. B., 378
MAINLAND, DONALD: Measurement of bone density. Bias and variation due to radiographic and photometric techniques, 115
MANHEIMER, R. H., 399
*MANKLE, E. A., 409
MARCUS, STANLEY: *see* LEVIN, MELVIN H., etc., 233
——, *409
Marie-Strümpell spondylitis with nodules, 271
*MARGOLIS, H. M., 409
MARKOWITZ, M., 390
MASON, H. L., 392
*MASON, R. M., 263
MAYNE, J. G., 61, 392
MEANOCK, R. I.: *see* FEARNLEY, G. R., etc., 134
MERCHANT, W. R., 399
Metabolism, adaptation in animals, *78
——, aspirin and, 385
MEXICO, INSTITUTE OF CARDIOLOGY:
Ist International symposium on Rheumatic Fever, 1956, 181
MEYER, K., 66, 68
MIELKE, J. E., 378
*MILCH, H., 78
MILLARD, J. B., and BARBER, H. STUART: Clinical trial of intravenous and intramuscular iron in arthritis, rheumatoid, 51
MILLER, R. D., 392, 393, *78
MONTGOMERY, M. M., 400, *409
MOORE, ROBERT: *see* HOLLANDER, JOSEPH L., etc., 320
MORE, R. H., 381
MORGAN, W. K. C.: *see* THOMAS, A. E., etc., 176
MOVAT, H. Z., 381
Mucoprotein estimation, 339, 342
*MUEHRCKE, R. C., 409
MURPHY, P. H., 387
Musculoskeletal nosology, *409
Myeloma, multiple, 271
Myocarditis and bovine gamma globulin, *79

N-acetyl-glucosamine, 357
Nail lesions in arthritis, 349
*NAUGLER, W. E., 409 *ter*
Necropsy of kidneys in gout, 61
—— of polyarteritis, 48
NEHER, G. M., 62
NEUSTADT, D. H., *78, *397, *409
*NEWMAN, M. K., 409
*NEY, J., 409
Nitrogen mustard, resistance to, *79
Nodule, fibrinoid in, 268
——, periosteal, histology of, 49
Nodules in Marie-Strümpell spondylitis, 271
——, subcutaneous, histology of, in polyarteritis, 46
Nosology, musculo-skeletal, *409
Nunemaker, J. C., 380

Obesity and joint disease in mice, 69
OBITUARY:
Mathieu-Pierre Weil, 373
O'CONNELL, D.: Ankylosing spondylitis. The literature up to the close of the nineteenth century, 119

OKA, MARTTI: Absorption of hydrocortisone from the joint cavity into the circulation, 327
*OLASH, F. A., 78
Ophthalmology and arthritis, rheumatoid, 22
*OSMOND-CLARKE, H., 263
Osteo-arthritis, diagnosis of, 7
—— in females, 81
——, hydrocortisone and procaine injection in, 330
——, —— acetate and joint temperature in, 320
——, —— *ter*-butyl acetate in, 258
—— and personality disorder, *78
——, prednisone and joint temperature in, 320
—— and psoriasis, 354
——, radiology of, 333
——, rehabilitation in, 399
——, symptoms of, 399
—— and uveitis, 144
Osteo-arthropathy, hypertrophic, in polyarteritis, 46
Osteo-arthrosis ("iatrogenic arthritis"), *78
Osteoporosis, incidence of, 8
——, radiology of, 55
*OWENS, J. N., JR., 409 *bis*

*PATTON, F., 78
PAYNE, R. W., *409 *bis*
PEACOCK, J. H., 265
*PEAK, W. P., 409
PEARCE, R. H., 65, 67
PEARSON, C. M., 379
PECHET, M., 77
Penicillin prophylaxis of streptococcal epidemics, 389
PENNEYS, RAYMOND, and SMUKLER, NATHAN M.: Changes in the intra-articular temperature of the knee with cutaneous vasoconstriction and vasodilatation of the toes in normal subjects, 241
——, *78
Pericarditis and arthritis, rheumatoid, 176
Periostitis in polyarteritis, 46
*PERSONS, E. L., 408
PETERSON, R. E., 76
Phenylbutazone in arthritis, rheumatoid, *409
—— in gout, 407
—— in musculoskeletal disorders, *409
—— in spondylitis, ankylosing, *409
Photometry of bone density, 115
Physiotherapy, World Confederation of: II International Conference on Physiotherapy, 1956, 83
PIGMAN, W., 67, *78, 379
*PILZ, C. G., 409
*PIRANI, C. L., 409
*PLATT, D., 78
PLOTZ, C. M., 384, 385, *409
Plasma cells in collagen disease, 381
—— —— in marrow and plasma globulin, 223
—— corticoid studies in arthritis, rheumatoid, *79, 392
—— fibrinogen estimation, 339
—— volume, 153
—— 17-hydrocycorticosteroid levels and salicylate therapy, 71
—— —— determination, 327
*POLLAK, V. E., 409 *ter*
POLLEY, H. F., 392, *408
Polyarteritis and osteo-arthropathy, hypertrophic, 000
—— nodosa and uveitis, 148
Polymerization of hyaluronic acid, 357
Polyphoretin as hyaluronidase inhibitor, 359
Polysaccharide, protein-bound, 339
—— of serum euglobulin fraction and agglutination test in arthritis, rheumatoid, 74
POPERT, A. J., 410
Population survey of arthritis, rheumatoid, 1
POSKANZER, D. C., 389
POSKE, R. M., 400
Prednisolone acetate, intra-articular, *408
—, intra-articular, *78
——, ——, in osteo-arthritis, 320
—— and erythrocyte sedimentation rate, 360
—— and gastric secretion, 397
—— and synovial fluid viscosity, 360
Prednisone, 81
—— in arthritis, rheumatoid, *78, *409 *bis*
Pregnancy and lupus erythematosus, *409
Procaine, intra-articular, and hydrocortisone in arthritis, rheumatoid, 134
——, ——, in osteo-arthritis, 330
Prophylaxis of rheumatism, acute, 35
—— of streptococcal epidemics, 389
Protein in synovial fluid, 378
Protein-bound polysaccharide estimation, 339
PRUNTY, F. T. G., 411
Psoriasis and arthritis, 348
——, familial, 349
——, laboratory investigation of, 353
—— and uveitis, 148
Psychology of arthritis, rheumatoid, 272
Psychosomatic study of children with arthritis, 398
*PULOS, P., 409 *bis*
Purine biosynthesis, 404

QUIN, C. E.: *see* LEVEAUX, V. M., etc., 330

Radiographs in measurement of bone density, 115
Radiology of arthritis, rheumatoid, 55
—— of osteo-arthritis, 333
—— of osteo-arthropathy in polyarteritis, 47
—— in a population sample, 3
—— of spondylitis, ankylosing, 41
—— of Still's disease, 298
RAGAN, C., 65, 383
Rats, arthritis in, 379
Raynaud's phenomenon and uveitis, 148
*REEDER, P. S., 409
Rehabilitation, 271
—— of arthritics, 399
Reiter's syndrome, muco-cutaneous lesions in, 400
—— —— and uveitis, 148
REJHOLEC, V.: *see* WAGNER, V., etc., 364
Resorcidin turbidity test, 339
Rheumatic fever: *see* Rheumatism, acute
Rheumatism, acute, anti-body response in, 364
——, ——, and carditis, 164, 166
——, ——, electrophoresis in, 387
——, ——, immunology of, 364, 386
——, ——, incidence of, 33, 160
——, ——, modern trends in, 33
——, ——, mortality from, 33
——, ——, penicillin prophylaxis of, 390
——, ——, and psoriasis, 354
——, ——, serum proteins in, 82
——, ——, sialic acid test for, 387
Rheumatoid arthritis: *see* Arthritis, rheumatoid
RICHMOND, J., GARDNER, D. L., ROY, L. M. H., and DUTHIE, J. J. R.: Nature of anaemia in rheumatoid arthritis. III. Changes in the bone marrow and their relation to other features of the disease, 217
——: *see* ALEXANDER, W. R. M., etc., 12
*RICHTER, M. N., 409
*RINEHART, R. E., 409
RIVELIS, A. L., 397
ROBINSON, H. S., 400
ROBINSON, W. D., 67, 71
RODNAN, G. P., 73, 391, 398
ROPES, M. W., 68, 379, 401
ROSEMAN, S., 67
ROY, L. M. H.: *see* ALEXANDER, W. R. M., etc., 12
——: *see* RICHMOND, J., etc., 217
——, 266
RUBIN, T., 399

SALA, G.: *see* VILLA, L., etc., 237
Salicylate and pituitary-adrenal system, 71, *78
—— in rheumatism, acute, 366
—— therapy mediated by steroids, *409
SAVAGE, O., 410
Scarlet fever, incidence of, compared with rheumatism, acute, 167
*SCHAFFARZICK, R. W., 409 *ter*
SCHMID, FRANK R.: *see* ZIFF, MORRIS, etc., 227
SCHMID, K., 378
SCHREINER, G. E., 73
*SCHUBERT, M., 78 *bis*
SCHUIT, H. R. E.: *see* KIEVITS, J. H., etc., 211
Scleroderma and arteritis, renal, *409
——, cortisone in, *409
——, diffuse, kidney involvement in, 73
——, ——, synovial lesions in, 398
SCOTT, D. G., 265
SCOTT, G. B. D.: *see* LOVELL, R. R. H., etc., 46
SEED, J. C., 386
SEEGMILLER, J. E , 61
*SEIFTER, J., 78
SELIN, G., 399
Serology, 268, 26º *bis*, 270
—— of arthritis with psoriasis, 353
—— ——, rheumatoid, 266 *bis*, 381, 382, 383, 384

Serology in population sample, 3
—— of rheumatism, acute, 365
—— of sensitized human cells, 246
—— of steroid therapy, 338
Serum complement titres in diagnosis of collagen disease, 74
—— euglobin precipitation, *408
—— gamma-globulin, 383
—— hexosamine estimation, 339, 343
—— mucoprotein estimation, 269, 339, 342
—— protein electrophoresis, *409
—— —— in rheumatism, acute, 82
—— polysaccharide electrophoresis, 387
—— resorcidin turbidity test, 339
—— uric acid, determination of, *409
—— —— —— and uricase, 268
Sexual maturity in Still's disease, 313
SHARP, J., 81, 386
——: *see* STANWORTH, A., etc., 140
SHORT, C. L., 374
Shoulder, painful, hydrocortisone in (film), 270, *410
*SHULMAN, L. E., 409
*SICKLEY, J. F., 409
SIGLER, J. W., 395
SIKES, D., 62
SILBERBERG, M., 69
SILBERBERG, R., 69
SINGER, J., 384
Sjögren's syndrome, 21, *78
Skin lesions in arthritis, 349
—— tests of corticosteroids, *78
SLOCUMB, C. H., 392
*SMITH, C., 79
SMITH, R. T., 64, 65, 395, *409
*SMUKLER, N. M., 78
——: *see* PENNEYS, RAYMOND, etc., 241
SMYTH, C. J., 64, 75, 406
SNYDER, A. I., *79, 398
Social factors in decline of rheumatism, acute, 37, 168
Sociedad Española del Reumatismo: *see* Spain
Società Italiana di Reumatologia: *see* Italy
Société Canadienne de Rhumatologie: *see* Canada
SOCIETIES:
American Rheumatism Association, 61, 374
Arthritis and Rheumatism Foundation, 410, 412
Australian Rheumatism Council, 191
Canadian Rheumatism Association, 267
Empire Rheumatism Association, 83, 183
Heberden Society, 81, 189, 263, 410
Ligue Internationale contre le Rhumatisme, 83, 267
Mexican Institute of Cardiology, 181
Sociedad Española del Reumatismo, 188
Società Italiana di Reumatologia, 82, 182
Société Canadienne de Rhumatologie, 267
World Confederation of Physiotherapy, 83
SOKOLOFF, L., 408, 409
South Wales, arthritis in a population survey, 59
SPAIN: Sociedad Española del Reumatismo, 188
Spondylitis and heart disease, 81
——, rehabilitation in, 399
——, and uveitis, 147
——, ankylosing, in adults after juvenile arthritis, rheumatoid, 40
——, ——, differential diagnosis of, 386
——, ——, history of, 119
——, ——, phenylbutazone in, *409
STANWORTH, A., and SHARP, J.: Uveitis and rheumatic diseases, 140
STARNES, W. R., 69
STECHER, R., 65
*STECK, I. E., 409 *ter*
STEINBROCKER, O., 394, 400, *409
Steroid glucuronide foundation, *78
—— therapy, laboratory aids in, 338
—— —— of lupus erythematosus, 400
Steroids in human blood, 269
STETTEN, D., JR., 61, 404
Still's disease, growth in, 295
—— ——, prognosis of, 263
STOLLERMAN, G. H., 390
*STOLZER, B. L., 409
STONE, S. S., 76
STRANGE, DAVID: *see* LEVIN, MELVIN H., etc., 233
Stress, 269
——, effects of, during ACTH therapy, 410
Streptococcus, group-A, and biosynthesis of hyaluronic acid, 378
——, haemolytic, in rheumatism, acute, 35
—— immunization in heart tissue, 386
——, penicillin prophylaxis of, 389
SUNDBLAD, L.: *see* EGELIUS, N., etc., 357
SWANSON, J. N., 62, 72
SWENSON, C. B., 62
SWEZEY, ROBERT L.: *see* LEVIN, MELVIN H., etc., 233
——, *409
Swine, rheumatoid disease in, 62
*SWINEFORD, O., JR., 79
Synovial fluid in arthritis, rheumatoid, 357
—— ——, electroconvection of, to isolate hyaluronic acid, 67
—— —— in osteo-arthritis, 322
—— ——, proteins in, 378
—— ——, source of, *78
—— ——, viscosity of, 358
—— membrane, histopathology of, *78
—— ——, metabolism of, 264
—— tissue, antigenicity of, 265
—— —— in diffuse scleroderma, 398
S^{35}-labelled materials separated from cartilage and bone by chromatograph after administration of sodium sulphate-S^{35}, 68
—— fixation in stomach of hypophysectomized rats, hydrocortisone and growth hormone and, *409

*TANZ, R. D., 79
*TEGNER, W. S., 263
Temperature, intra-articular, in osteo-arthritis, 320
——, ——, and vasodilatation and constriction of extremities, *78, 241
Tendonitis, calcified, and cardiovascular disease, *409
TERRY, R., 408
Therapy, evaluation of, *409
THOMAS, A. E., and MORGAN, W. K. C.: Pericarditis complicating arthritis, rheumatoid, 176
THOMAS, D. P. PAGE, 264
THOMPSON, MALCOLM, and EADIE, STELLA: Kerato-conjunctivitis sicca and rheumatoid arthritis, 21
*THRIFT, C. B., 409
*TRAUT, E. F., 409
Turbidity test, 339
Twins, arthritis, rheumatoid, in, *409
——, Still's disease in, 299

Ultra-sound and Hypospray in hydrocortisone injection, *409
United States of America: *see* American Rheumatism Association; Arthritis and Rheumatism Foundation
Uricosuria in gout, 406
URIST, M. R., 72
Uveitis and rheumatic disease, 140

*VASSITIS, J., 409
VAUGHAN, J. H., 383, 385, 388, 394, *410
Vertebra, lipping of, 268
VILLA, L., SALA, G., and BALLABIO, C. B.: Clinical and metabolic effects of Δ^1-dehydro-9-alpha-fluoro hydrocortisone acetate, 237
Viscosity test, 357

Waaler-Rose reaction with sensitized human cells, 246
WAGNER, V., and REJHOLEC, V.: Response by antibodies to tissue antigens in the course of rheumatic fever, 364
*WALLACE, S. L., 410
*WALLER, M. V., 410
WARD, L. E., 392
WARREN, J. E., 66, 70, *79, 380, 391, 392
WATSON, D. R., 67
*WECHSLER, R., 409
WEDGWOOD, R. J., 74
Weight of children with Still's disease, 295
WEINBERGER, H., 380, *409
*WEINER, A. D., 408
*WEISS, L. P., 79
WEST, H. F.: Acquired resistance to corticotropins, 124
——, 81
WHEDON, G. D., 76
*WICHELHAUSEN, R. H., 409
WILLETT, F. M., 396
WILLIAMS, A. WYNN: *see* AITCHISON, J. D., etc., 26
WILLIAMS, R. R., 65, 76
WILSON, H., 70, 72, *410
WRIGHT, V.: Psoriasis and arthritis, 348
——, 82
Wrist involvement in Still's disease, 310
WU, C., 392
WYNGAARDEN, J. B., 391, 393

YIELDING, K. L., 76
*YÜ, T. F., 410

ZIFF, MORRIS, CONTRERAS, VINCENT, and MCEWEN, CURRIER: Spondylitis in post-pubertal patients with rheumatoid arthritis of juvenile onset, 40
——, ——, and SCHMID, FRANK R.: Use of the hypospray jet injector for the intra-articular and local administration of hydrocortisone acetate, 227
——, 64, 67, 76, 78, 382, 384, 400, *410 *bis*

ZUCKNER, JACK, MACHEK, OTAKAR, and AHERN, ARCH M.: Hydrocortisone *tertiary*-butylacetate for intra-articular therapy in rheumatic diseases, 258

4-amino-5-imidazolecarboxamide-C^{13} in uric acid in gout, 61
9-α-fluoro hydrocortisone and heart muscle electrolytes, *79
17-hydroxycorticoid, diurnal urinary excretion of, 69
17-ketosteroid, diurnal urinary excretion of, 69
—— excretion in gout, 264

INDEX TO SUBJECTS OF ARTICLES ABSTRACTED

* indicates that only the title of the article is given.

Acetabulum, protrusion of, in arthritis, rheumatoid, *200
Acid, acetylsalicylic, in rheumatic carditis, 85
——, hyaluronic, viscosity of, in synovial fluid, 288
——, uric, clearance in gout, 203
——, ——, fate of, *98
——, ——, in plasma, phenylbutazone and, 98
ACTH in arthritis, rheumatoid, *113, 196, 199, 417, 418
—— in bronchial asthma, 209
—— in carditis, rheumatic, 85, 106
—— in children, 209
—— in chorea minor, 87
——, eosinophil response to, 108
——, failure of, in rheumatism, acute, with recurrent streptococcal infection, 90
—— and gastric secretion, 111
—— and inflammation, aseptic, 208
——, intravenous infusion of, 108
—— in lupus erythematosus, 205, 423
—— and metabolism of neutral 17-corticosteroids, 109
—— and nephrotic syndrome, 107, 426
—— in oedematous exophthalmos, 293
—— and osteoporosis, 112
—— in pemphigus, 290
—— and plasma concentrations of vitamin A, carotene, and tocopherols, *90
—— in pneumonia, 94
—— in rheumatism, acute, *195, 273, 277, 416
—— in scleroderma, 205
——, sodium content, and body weight, *195
—— in Still's disease, 95, 197, *200
—— in synovitis of hip, *427
—— in thyroiditis, 426
Acute rheumatism: *see* Rheumatism, acute
Adrenal cortex function in Sydenham's chorea, 87
—— ——, indices of function of, 109
—— cortical function in hypothermia, 292
—— crisis, 425
Adrenalectomy, metabolic response to, 293
—— and Cushing's syndrome, 425
Adrenocortical hormone estimation in rheumatism, acute, 276
Aetiology of rheumatic disease, *285
Agglutination reaction, *106, *424 *ter*
——, streptococcal, in arthritis, rheumatoid, 104
——, ——, and indirect lysis of erythrocytes, *417
α-tocepherol in Dupuytren's disease, *202
Aldosterone, *201, 293, *294
Allergy, steroid therapy of, 110
Amidopyrine in formalin arthritis, *106
—— gentisate, *202
Amodiaquin: *see* Camoquin
Amyloid in arthritis, rheumatoid, 418
Ankylosing spondylitis: *see* Spondylitis, ankylosing
Anticoagulants, acquired, in circulation in collagen disease, 98
Antihyaluronidase titre in rheumatism, acute, 274
Antimalarials in discoid lupus erythematosus, 285
——, synthetic, in lupus erythematosus, 99
Antistreptolysin-O titre, *207 *bis*, *289, *424
—— —— in diagnosis of rheumatism, acute, 273, 274
—— —— in pain assessment, 273
—— —— in rheumatic endocarditis, *90
—— —— in rheumatism, acute, 416, *417
Aponeurotic tissue, lesions of, 105
Aortitis with ankylosing spondylitis, 281
Arteritis, rheumatic coronary, 282
Arthritis, activity, estimation of, 419
——, epidemiology and classification of, *98
——, insulin shock in, 201
——, cervical traumatic, *285
——, chronic, serology of, *207
——, experimental, gold salts in, *421
——, ——, in rats treated with pyrazolidin and amidopyrine, *106
——, rheumatoid, ACTH, long-acting, in, 196, 199, 417, 418
——, ——, aetiology of, *419
——, ——, amyloid in, 418
——, ——, arterial route therapy, *419
——, ——, aspirin compared with cortisone in, 195
——, ——, auto-antibodies in, 206
——, ——, bone marrow in, 277
——, ——, calcium gluconate infusion in, *279
——, ——, clinical ages after 20 years, *202
——, ——, Congo red test in, 418, *419
——, ——, cortisone in, 91 *bis*, *279
——, ——, ——, long-acting, in, 417, 418
——, ——, diagnosis of, *199
——, ——, in the elderly, *419
——, ——, electrophoresis in, *200, 279, *419
——, ——, glycine metabolism in, 102
——, ——, gold in, *95, 196, *199
——, ——, —— and bismuth per rectum in, *98
——, ——, hexamethonium chloride in, 94
——, ——, hip in, *419
——, ——, history-taking in, *202
——, ——, hydrocortisone in, 196, *279 *bis*
——, ——, hypophyseal abnormalities in, 279
——, ——, incidence of, *203
——, ——, inhibition by essential hypertension, *95
——, ——, joint immobilization in, 418
——, ——, —— lesions in, 94
——, ——, juvenile, 90
——, ——, ——, spondylitis of, 281
——, ——, kidney involvement in, 279
——, ——, liver function tests in, *200, 417
——, ——, lung lesions in, 197
——, ——, mepacrine in, 198, *199
——, ——, nitrogen mustard in, 94, *199
——, ——, orthopaedic management of, *200
——, ——, P.A.S. in, *279
——, ——, phenylbutazone in, 97
——, ——, pigmentation in, *280
——, ——, pleural effusion in, 278
——, ——, prednisone in, 91, 92 *bis*, 93 *quater*, *95, 199, *200, 278 *bis*, *279 *bis*, 292, *419, *420
——, ——, protrusio acetabuli in, *200
——, ——, psychosocial factors in, *95
——, ——, rehabilitation of, 95 *bis*, 198 *bis*, *199, *202, 278
——, ——, reserpine in, 283
——, ——, resochin in, 198
——, ——, serology of, *106 *ter*
——, ——, serum factor in, 104
——, ——, silicosis and, *199
——, ——, skin ulceration in, 196
——, ——, sodium pyrocatechol-3-carboxylate in, 91

Arthritis, rheumatoid, steroid therapy in, *113, *279
——, ——, succinate-salicylate in, *202
——, ——, sulphur in, *95
——, ——, synovectomy of knee in, 196
——, ——, synovial fluid in, *106, 288
——, ——, teleradiotherapy of, *95
——, ——, thyroid tissue implantations in, *98
——, ——, visceral lesions in, *419
——, ——, Waaler-Rose reaction in, 419
——, sacro-iliac, in ankylosing spondylitis, *200
Arthrography of hip, *200
Arthrosis of hand and wrist, *200
—— and liver function, *207
Aspirin compared with cortisone in arthritis, rheumatoid, 195
—— and prednisone, *421
—— in rheumatism, acute, *417
Atebrin: *see* Quinacrine
Aureomycin in prophylaxis of acute rheumatism, *90
Auto-antibodies in arthritis, rheumatoid, 206

Bacteria, throat, in chemoprophylaxis of rheumatism, acute, 276
Beta-glucuronidase in synovial fluid, 206
——-haemolytic streptococcal infections, penicillin in, 87
Bile as suppressive agent, *288 *bis*
Biologic false positive reactors in lupus erythematosus, 100
Bismuth in arthritis, rheumatoid, *98
Blood, phenylbutazone and, *201 *bis*
—— groups and rheumatism, acute, *417
Bone-marrow findings, *289
Brazil, rheumatism, acute, in, *195
Bronchial asthma, ACTH in, 209

Calcium gluconate infusion in arthritis, rheumatoid, *279
Camoquin in discoid lupus erythematosus, 285
Capillary fragility, 207
Carbohydrate, protein-bound, in rheumatism, 103
Cardiovascular system and phenylbutazone, *114
Carditis, ACTH in, 106
——, rheumatic, acetylsalicylic acid, corticotrophin, and cortisone in, 85
——, ——, antistreptolysin-O titre in, *417
——, ——, cortisone in, 86, 193
——, ——, C-reactive protein in, 277
——, ——, hydrocortisone in, 193
——, ——, mechanical and myocardial factors and mitral stenosis, 85
——, ——, prednisone in, 84
——, ——, prophylaxis of, 84
——, ——, respiration in, 413
——, ——, silent, radio diagnosis of, in childhood, 86
——, ——, subclinical, *277
——, ——, valvular thickening in, 413
——, rheumatoid, death due to, *417
Carotene in plasma and ACTH therapy of rheumatism, acute, *90
Cartilage, physiology of, 427
Chemotherapy of rheumatism, acute, *417
Children, ankylosing spondylitis in, *417
——, arthritis, rheumatoid, in, 90, *195 *ter*
——, growth of, and cortisone, 424
——, radiodiagnosis of silent rheumatic carditis in, 86
——, rheumatic, tonsillectomy in, *277
——, rheumatism in, hormone and salicylate therapy compared, 414
Chloroquine in lupus erythematosus, *102
Chondroitin sulphate, non-antigenicity of, 206
Chorea minor, ACTH in, 87
—— ——, cortisone in, 87
Codeine phosphate, *202
Colcemid in gout, 204
Collagen disease, auto-immune thromboplastin deficiency, 98
——, soluble, *208
Collagenosis, viscero-cutaneous, 101
Congo Red test in arthritis, rheumatoid, 418, *419
Cornea, lesions of, caused by cortisone, *293
Cortisone, antipyretic action of, 111
—— in arthritis, rheumatoid, 91 *bis*, *113
—— —— ——, compared with aspirin, 195
—— in carditis, rheumatic, 85, 86, 193
—— in children, 209
—— in chorea minor, 87
——, corneal lesions after, *293
——, eosinophil response to, 108
—— in exophthalmos, oedematous, 293
—— in histoplasmosis, experimental, *113
——, indications for, *427
—— and inflammation, aseptic, 208
—— in keratitis, parenchymatous, *293
——, long-term, 199, 417, 418
——, ——, effects on growth of children, 424
—— in lupus erythematosus, 205, 423
—— metabolites in synovial fluid, *293
Cortisone in nephrotic syndrome, 107, 426
—— in osteo-arthritis, spinal, 280
——, osteoporosis and, 112
——, overdosage, *200
—— in pemphigus, 290, 292
—— in pneumonia, 94
—— in polyarthritis, subacute, in adults, 85
—— and protein metabolism, 425
—— in rheumatism, acute, 195, 273, 277, 416 *bis*
—— in scleroderma, 205
—— in scleromalacia perforans, 112
—— in Still's disease, 95, 197, *200
—— in thyroiditis, 426
——, withdrawal of, 112
—— and 17-ketosteroid metabolism, 109
Corticosteroids, analysis of, 290 *bis*
Corticotherapy, continuous, *427
C-reactive protein, 205, *207 *bis*
—— —— and carditis, rheumatic, 277
—— —— and spondylitis, ankylosing, 96
Cushing's syndrome, 425
—— ——, 9-α-fluoro hydrocortisone and, 109
Cutaneo-articular syndrome, *202

Delta cortene: *see* Prednisone
Deltacortril: *see* Prednisone
Demecolcine (Colcemid) in gout, 204
Dental aspects of rheumatism, *202
Deoxycortone in rheumatic disease, *114
De Quervain's disease, hydrocortisone in, 107
Dermatomyositis, 101
Desacetylmethyl colchicine in gouty arthritis, 203
Diacetyl-3-carboxyl acid and prednisone in arthritis, rheumatoid, *420
Diagnosis of arthritis, rheumatoid, *199
—— of lupus erythematosus, 422
—— of rheumatism, acute, *195, *195 *bis*
——, radiological, of silent rheumatic carditis in childhood, 86
Diphenylamine reaction, *106 *bis*, *207 *bis*
Diphosphopyridin nucleotide and niacin furfuryl reaction in arthritis, rheumatoid, *208
Disk, lumbar, discography of, 285
Dupuytren's contracture, *98
—— disease, familial, α-tocepherol in, *202

Electrocardiograph in Reiter's syndrome, *202
—— in rheumatism, acute, 276
Electro-encephalogram in chronic rheumatism, *202
Electrophoresis in arthritis, rheumatoid, *200, *419
—— in endocarditis, rheumatic, *90
—— of plasma proteins during mud pack therapy, 207
—— —— —— in children, *207
—— of serum proteins, *106
—— of synovial fluid, *106
Endocarditis, residual, prevention of by hormone therapy, 274
——, rheumatic, antistreptolysin titre in, *90
——, ——, electrophoresis in, *90
——, ——, incidence of, *90
——, ——, tissue-specific serum antibody in, 103
Endocrine origin of rheumatism, *421
Enzyme glutamic oxalacetic transaminase in serum in rheumatism, acute, 193
Eosinophil response to steroid therapy, 108
Erasol: *see* Nitrogen mustard, 94
Erythema marginatum and rheumatism, acute, 194
Erythrocyte determination, 424
—— sedimentation rate in diagnosis and prognosis, 105
Eye, diseases of, and rheumatism, *114 *ter*, 284, 285
—— in Still's disease, 419
Exophthalmos, oedematous, steroid therapy for, 293

Felty's syndrome, *279 *bis*
——, keratitis and scleritis with, 279
Fibrinogen clot density in rheumatism, acute, 103
—— polymerization test, 105
Fiessinger-Leroy-Reiter syndrome, *200, *201
—— —— —— and spondylitis, ankylosing, 96, *97, *281, *282
Flexin, 420
Focal infection, *202, *421

Galen on rheumatism, *421
Gastric lesions after phenylbutazone, 113 *bis*
Genito-urinary infections and ankylosing spondylitis, *97
Glucone, hypertonic, and salicylate therapy of arthritis, rheumatoid, 194
Glycine metabolism in arthritis, rheumatoid, 102
Gold in arthritis, rheumatoid, *95, *98, 196, *199
—— and liver function, *207

Gold salts per rectum in experimental arthritis, *421
Gout, demecolcine in, 204
——, desacetylmethylcolchicine, 203
——, metabolism in, *98
——, observations in 520 patients, 203
——, phenylbutazone in, 98
——, relief of, 203
——, uric acid clearance in, 98 *bis*, 203
Granulocytopenia after phenylbutazone, *114

Haematemesis after phenylbutazone, 97
Haemorrhage, retinal, in Fiessinger-Leroy-Reiter's syndrome, *201
Haemorrhagia, prednisone in, 426
Hand, arthrosis of, *200
——, polyarthritic, 197
Heart block in rheumatism, acute, *277
—— disease: *see* Carditis
—— in spondylitis, ankylosing, *282
Heredity in joint disease, *98
—— —— rheumatism, *202
—— of spondylitis, ankylosing, 200, *200
Herpes zoster ophthalmicus and periarteritis nodosa, 287
Hexamethonium chloride in arthritis, rheumatoid, 94
Hip in arthritis, rheumatoid, *419
——, arthrography of, *200
——, diagnosis of limitation of movement, *201
——, synovitis of, ACTH in, *427
Histamine-eosinophil test, *289
Histoplasmosis, experimental, cortisone in, *113
Hormone production and salicylates, *421
—— therapy in rheumatism, acute, *195
—— —— in Sydenham's chorea, 87
—— —— compared with salicylate, 414
—— ——, value of, *294
Humoral changes, *202
Hydrocortisone in arthritis, rheumatoid, 196, *199, *279 *bis*
—— in carditis, rheumatic, 193
—— in exophthalmos, oedematous, 293
—— in lumbago, *294
—— in lumbosciatica, *421
—— in neuralgia, *294
—— in painful shoulder, 289
—— metabolites in synovial fluid, 293 *bis*
—— in peri-arthritis of shoulder, 107
—— and prednisone, *294
—— in de Quervain's disease, 107
—— and synovial fluid protein electrophoresis, *106
——, intra-articular, 209, 291, *294 *bis*, *427 *quater*
——, intravenous, 107
—— *ter*-butylacetate, intra-articular, 107
Hyperkinesia in cerebral rheumatism, 428
Hypertension, essential, and inhibition of arthritis, rheumatoid, and malignant disease, *95
Hypophysis, abnormalities of, in arthritis, rheumatoid, *279
Hypophysectomy, metabolic response to, 293
Hypothermia, adrenocortical function in, 292

Industry, rheumatic disease in, *285
Infants, rheumatism, acute, in, *195, *417
Insulin shock in arthritis, 201
Iritis in spondylitis, ankylosing, *200, 281

Joint disease, heredity in, *98
—— ——, infections and, *98
—— lesions in arthritis, rheumatoid, 94

Keratitis in Felty's syndrome, 279
——, parenchymatous, cortisone in, 293
Kidney in arthritis, rheumatoid, 279
—— in lupus erythematosus, 99
—— function and cortisone therapy of rheumatism, acute, *195
Knee, biopsies of, 94
—— joint, radioactive sodium clearance from, 420
——, synovectomy of, in arthritis, rheumatoid, 196

Leukaemia after radiotherapy of spondylitis, ankylosing, 96
"Linidox", *202
Liver function in arthritis, rheumatoid, *200 *bis*, 417
—— —— and arthrosis, *207
—— —— and gold therapy, *207
Low back pain, 201
Lumbago, vertebral manipulation for, 288
——, hydrocortisone in, *294
Lumbar pain, *97
Lung lesions in arthritis, rheumatoid, 197
—— —— in lupus erythematosus, 101
Lung lesions in polyarteritis nodosa, 102
Lupus erythematosus, aetiology of, 100
—— ——, antimalarials in, 99
—— —— cell test, 100
—— —— ——, formation of, 422
—— ——, chloroquine and plasma 17-hydroxycorticosteroid levels in, *102
—— ——, kidney in, 99
—— ——, mepacrine in, 423
—— —— phenomenon, 204
—— ——, pulmonary lesions in, 101
—— ——, quinacrine in, 100
—— ——, radiology of, 99
—— ——, discoid, 422
—— ——, ——, antimalarial treatment of, 285
—— ——, disseminated, psychology of, *423
—— —— profundus, 287
—— ——, ——, diagnosis of, 422
—— ——, systemic, neuritis in, 422
—— ——, ——, prednisone in, 286
—— ——, ——, skin histology in, 423
—— ——, ——, steroid therapy in, 205
Lysozyme in rheumatism, acute, *106

Manipulation, vertebral, 284, 288
Marfan's syndrome, cardiovascular aspects of, *285
Marrow, bone, in arthritis, rheumatoid, 277
Menopause, early artificial, and rheumatic disease, 283
Mepacrine in arthritis, rheumatoid, 198, *199
—— in lupus erythematosus, 423
Methyl salicylate, topical, *202
Metacortandracin: *see* Prednisone
Meticorten: *see* Prednisone
Migraine, ophthalmic, and Dupuytren's disease, *202
Mitral commissurotomy and cardiac lesions, 276
—— valvoplasty and rheumatic activity, 194
Mud packs and electrophoresis in arthritis, rheumatoid, 207
Muscle, striated, histology of, in collagen disease, *423
Myelofibrosis, 427
Myelography in sciatica, *285

Nephritis, infective, and rheumatism, acute, *417
Nephrosis, prednisone in, 426
——, ACTH in, 107, 426
——, cortisone in, 107, 426
Nerve root lesions, cervical, and finger joint swellings, 284
Neuralgia, hydrocortisone in, *294
Neuritis and lupus erythematosus, 422
"Nevaquin: *see* Chloroquine
Niacin furfuryl reaction modified by diphosphopyridin nucleotide, *208
Nicotinic acid (tetrahydrofurfurylic ester) as skin test, *202
Nitrogen mustard in arthritis, rheumatoid, 94, *199

Obesity and joint disease, *280
Ophthalmology and collagen tissue, 287
—— of osteitis deformans, 97
—— of periarteritis nodosa, 287 *bis*
——, prednisone in, 112
Osteitis deformans, 97
Osteo-arthritis, *420
——, aetiology of, *200
——, cortisone in, 280
—— in the elderly, *200
—— of fingers, *200
—— as a metabolic disorder, *95, *200
——, reserpine in, 283
——, spinal, 280
——, ——, surgery of, *280
——, synovial fluid viscosity in, 288
Osteo-arthropathy, pulmonary hypertrophic, reversal of, by vagotomy, 428
Osteogenesis imperfecta, history of, 294
Osteomyelosclerosis, 427
Osteopathy, senile, 112
Osteopsathyrosis: *see* Osteogenesis imperfecta

Paget's disease: *see* Osteitis deformans
Pain, joint, assessment of, 273
——, lumbar and sciatic and spondylolisthesis, *97
para-aminobenzoic acid in rheumatism, acute, 277
PAS in arthritis, rheumatoid, *279
Pemphigus, steroid therapy of, 290, 292
Penicillin, benzathine, G, in beta-haemolytic streptococcal infections in children, 87
——, ——, intramuscular, in prophylaxis of rheumatism, acute, 87, 89, 194, 415

Peptic ulcer and ACTH, 111
Peri-arteritis nodosa, 101, *102, 204
Periarteritis nodosa and endomyocardial sclerosis, 423
—— ——, muscle histology in, *423
—— ——, ophthalmology of, 287
—— ——, pulmonary, 205
—— —— zoster, cerebral, with herpes zoster ophthalmicus, 287
——, scapulo-humeral, psychosomatic medicine in, *202
——, ——, diagnosis of, *202
Peri-arthritis of shoulder, *203
—— ——, hydrocortisone in, 107
—— —— in pulmonary tuberculosis, *423
——, ——, radiology of, *288
——, ——, of thoracic and pleuro-pulmonary origin, *98
Pericardium in rheumatism, acute, *417
Phagocytosis in connective tissue disorder, *106
Phenylbutazone, *202
—— in arthritis, rheumatoid, 97, *200
—— and blood clotting, *201 *bis*
—— and cardiovascular system, *114
——, gastric haemorrhage and, 113 *bis*
—— in gout, 98
——, granulocytopenia after, *114
——, haematemesis after, 97
——, intra-articular, 283
——, low dosage of, 201
—— in rheumatism, acute, *200, 277
—— in spondylitis, ankylosing, 97
——, Stevens-Johnson syndrome after, *114
—— and synovial fluid protein electrophoresis, *106
——, toxicity of, *201
Physiotherapy, 421
Pigmentation in arthritis, rheumatoid, *280
Plasma protein changes in rheumatism, acute, 414
—— uric acid in gout and phenylbutazone, 98
—— vitamin A, carotene, and tocopherols in acute rheumatism during ACTH therapy, *90
—— 17-hydroxycorticosteroids in rheumatism, acute, 89
Pleural effusion in arthritis, rheumatoid, 278
Pneumonia during steroid therapy, 94
Pneumonitis in rheumatism, acute, 414
Polyarteritis nodosa, 102
Polyarthritis of hand, 197
——, subacute, in adults, response to cortisone, 85
——, tissue-specific serum antibody in, 103
Polymerization of fibrogen, 105
Porphyrin metabolism in rheumatism, acute, 89
Potassium in serum, *106
Prednisone, 111, 209, 291, 292, *294 *quater*, 425
—— and allergy, 110
—— in arthritis, rheumatoid, 91, 92, *bis*, 93 *quater*, *95, 199, *200, 278 *bis*, *279 *bis*, *419, *427
—— and aspirin, *421, *427
—— in carditis, rheumatic, 84
—— and C-reactive protein, *207
—— with diacetyl-3-carboxyl acid, *420
—— in Felty's syndrome, *279
—— and haemorrhagia, 426
—— and hydrocortisone, *294
——, intra-articular, 289, *427
—— in lupus erythematosus, 286
—— metabolism, 110 *bis*
—— in nephrosis, 426
—— in ophthalmology, 112
—— in rheumatism, acute, 90, 416
——, side-effects of, 93
Prophylaxis of rheumatism, acute, 87, 89, *90 *bis*, 194, *194, *195 *quinter*, 415
Protein metabolism and cortisone, 425
Psychosocial factors in arthritis, rheumatoid, *95
Purpura rheumatica, 202
Pyrazolidin in formalin arthritis, *106

Q-T interval in carditis, rheumatic, 275
—— —— in rheumatism, acute, *90
Quinacrine in lupus erythematosus, 100

Radiodiagnosis of carditis, silent rheumatic, in childhood, 86
Radiology of lupus erythematosus, 99
—— of peri-arthritis, scapulo-humeral, *288
—— of sciatica, *98
—— of spondylosis, *98 *bis*
Radiotherapy, *421
—— of spondylitis, ankylosing, and leukaemia, 96
Rehabilitation, 95 *bis*
Rehabilitation after arthritis, rheumatoid, 198 *bis*, *199, *202, 278
Reiter's syndrome, 96, 97, 97 *quater*, 285, *421
—— ——, electrocardiogram in, *202
Reserpine in psychogenic rheumatism, osteo-arthritis, and arthritis, rheumatoid, 283
Rheumatic fever: *see* Rheumatism, acute
Rheumatism and ocular affections, 284, 285
——, acute, ACTH in, 273, 277, 416
——, ——, activity of, 102
——, ——, antimyocardial antibodies in, 102
——, ——, antistreptolysin and antihyaluronidase titres in, 274
——, ——, antistreptolysin-O titre, *207, 416, *417
——, ——, ——, and cortisone and prednisone, 416
——, ——, aspirin in, *417
——, ——, bacteria of throat during chemoprophylaxis of, 276
——, ——, blood groups in, *417
——, ——, —— reactions in, *417
——, ——, in Brazil, *195
——, ——, capillary microscopy in, 275
——, ——, case-finding in, *90
——, ——, chemotherapy of, *417
——, ——, clearing factor in, 416
——, ——, cortisone in, 273, 277, 416 *bis*
——, ——, C-reactive protein in, *207, *208
——, ——, diagnosis of, 273
——, ——, electrocardiographs in, 276
——, ——, electrophoresis of, *106, *195, *207
——, ——, erythema marginatum and, 194
——, ——, fibrinogen clot density in, 103
——, ——, haemolytic streptococcus in, *106
——, ——, histology of, 205
——, ——, hormone therapy, *274 *bis*, 276
——, ——, —— and salicylate therapy compared, 414
——, ——, immunology of, in, 415
——, ——, in infancy, *417
——, ——, and infective nephritis, *417
——, ——, lysozyme in, *106
——, ——, as a military problem, *195
——, ——, penicillin benzathine G and sulphonamides in prophylaxis of, 87, 89
——, ——, pericardial changes in, *417
——, ——, phenylbutazone in, 277
——, ——, plasma proteins in, *90, 414
——, ——, pneumonitis in, 414
——, ——, post-operative reactivation of, *277
——, ——, prednisone in, 90, 416
——, ——, prophylaxis, 87, 89, *90 *bis*, 194, *194, *195 *quinter*, 275, 415
——, ——, Q-T interval in, *90, 275
——, ——, in Santiago, *195
——, ——, in Saskatchewan, *195
——, ——, serology of, 193, *194 *bis*, *195 *quater*
——, ——, serum electrophoresis in, *106, *195
——, ——, streptococcal agglutination and indirect lysis of erythrocytes in, *417
——, ——, —— culture, supernates in, *207
——, ——, —— infection in, 90
——, ——, treatment of, 88, 277, *277
——, ——, 17-hydroxycorticosteroids in, 89, 208
——, ——, 17-ketosteroids, urinary, in, 88
——, cerebral, 428
——, juvenile, *90
——, palindromic, synovial fluid in, *202
——, psychogenic, reserpine in, 283
——, tuberculous, *98
Rheumatoid arthritis: *see* Arthritis, rheumatoid
Rufus of Ephesus, rheumatism in works of, *114

Salicylamide, *202, 282
Salicylate and capillary fragility, *285
——, depot, *202
—— and hormone production, *421
—— and hormone therapy compared, 414
—— and prednisone, *427
—— in rheumatic disease, *114
—— in rheumatism, acute, 194, *195, 277
Salicylism, specific therapy, 282
Santiago, rheumatism, acute, in, *195
Saskatchewan, rheumatism, acute, in, *195
Sciatica, hydrocortisone in, *421
——, pain in, *97
——, radiology of, *98
——, vertebral manipulation for, 288
——, myelography in, *285
Scleritis in Felty's syndrome, 279
Scleroderma, 101
——, pulmonary manifestations of, 286
——, steroid therapy in, 205
Scleromalacia perforans, cortisone in, 112
Sclerosis endomyocardial and periarteritis nodosa, 423
Serology of arthritis, rheumatoid, *106 *ter*
—— of rheumatism, *202, 289, *289 *ter*, *424 *octem*
—— of rheumatism, acute, 193

Serology of spondylitis, ankylosing, *106, 281
Serum antibody, tissue-specific, in polyarthritis and rheumatic endocarditis, 103
—— cholesterol, *207
—— cholinesterase, *424
—— electrophoresis in rheumatism, acute, *195
—— factor in arthritis, rheumatoid, 104
—— lipids in arthritis, rheumatoid, *106
—— potassium and sodium in arthritis, rheumatoid, *106
—— proteins, electrophoresis of, *106
Shoulder, peri-arthritis of, hydrocortisone in, 107
—— hand syndrome and pulmonary tuberculosis, *423
——, painful, hydrocortisone in, 289
Silicosis and arthritis, rheumatoid, *199
Sjögren's syndrome, 284
Skin, histology of, in lupus erythematosus, 423
—— ulceration in arthritis, rheumatoid, 196
Sodium content and body weight after ACTH therapy for rheumatism, acute, *195
—— excretion, effect of ACTH on, in heart disease, 106
—— pyrocatechol-3-carboxylate in arthritis, rheumatoid, 91
——, radioactive, clearance from knee joint, 420
—— in serum, *106
Spine, cervical, 96
——, diagnosis of limitation of movement, *201
——, osteo-arthritis of, 280 *bis*
Spondylarthritis and Fiessinger-Leroy-Reiter's syndrome, *281, *282
Spondylitis, ankylosing, *200 *quinter*, 280
——, ——, aetiology of, *420
——, ——, aortitis in, 281
——, ——, C-reactive protein in, 96
——, ——, familial, 200, *200
——, ——, and Fiessinger-Leroy-Reiter's syndrome, *200
——, ——, genito-urinary infections and, *97
——, ——, heart in, 282
——, ——, iritis in, *200, 281
——, ——, juvenile, *417
——, ——, leukaemia after radiotherapy of, 96
——, ——, phenylbutazone in, 97
——, ——, and Reiter's syndrome, 96
——, ——, sacro-iliac arthritis in, *200
——, ——, serology of, *106, 281
——, cervical, and Dupuytren's contracture, *98
—— of juvenile, arthritis, rheumatoid, 281
Spondylochondrosis of cervical spine, 96
Spondylolisthesis and pain, *97
Spondylosis, pathology of, *98
——, age and radiology of, *98
——, radiology of, *98
Succinate-salicylate in rheumatism, *202
Sulphonamide in prophylaxis of rheumatism, acute, 87, 194
Sulphur in arthritis, rheumatoid, *95
Stenosis, mitral, in carditis, rheumatic, and mechanical and myocardial, 85
Stevens-Johnson syndrome after phenylbutazone, *114
Still's disease, hormone therapy of, 197, *200
—— —— with ocular complications, 419
—— ——, steroid therapy of, *95
Streptococcus, Group-A, 415
——, ——, in Sydenham's chorea, 413
—— haemolytic, in rheumatism, acute, *106
Streptococcal culture supernates, *207 *bis*
—— infection, recurrent, and ACTH therapy of rheumatism, acute, 90
Sydenham's chorea, abnormal adrenal cortex function in, 87
—— —— and Group-A streptococci, 413
—— ——, mental forms of, *277
Synovectomy of knee in arthritis, rheumatoid, 196
Synovial fluid in arthritis, rheumatoid, *106
—— ——, beta-glucuronidase in, 206
—— ——, electrophoresis of, *106, *202
—— ——, hydrocortisone and, *106, 293
—— ——, phenylbutazone and, *106
—— —— protein, *289
—— ——, viscosity of hyaluronic acid in, 288
Synovitis of hip, ACTH in, *427

Teleradiotherapy in arthritis, rheumatoid, *95
Tendon, degenerative lesions of, 105
Thiodiglycol, *202
Thromboplastin deficiency, 98
—— ——, auto-immune, in collagen disease, 99
Thyroid tissue implantation, *98
Thyroiditis, cortisone in, 426
Tocopherols in plasma and ACTH therapy of rheumatism, acute, *90
Tonsillectomy and arthritis, rheumatoid, *97, *98
—— in rheumatic children, *277
Transaminase, glutamic oxalacetic, 193
Trypsin, *421
Tuberculosis, pulmonary, and shoulder-hand syndrome, *423
Twins and study of rheumatism, 113

Uveitis, rheumatic origin of, 421

Vagotomy in osteo-arthropathy, pulmonary hypertrophic, 428
Vertebra, manipulation of, 284, 288
Vitamin A in plasma and ACTH therapy of rheumatism, acute, *90

Waaler-Rose reaction, *419, *424 *bis*
—— —— Heller reaction, *208
Wrist, arthrosis of, *200

Zone electrophoresis in serology of arthritis, rheumatoid, 279
Zoxazolamine (Flexin), 420

9-α-fluoro hydrocortisone acetate, 209, 290
—— —— —— in allergic disorders, 110
—— —— in Cushing's syndrome, 109
—— —— metabolism, 110
—— —— renal effect of, *427
17-hydroxycorticosteroids in rheumatism, acute, 208
—— in plasma in rheumatism, acute, 89
17-ketosteroid metabolism and steroid therapy, 109
——, urinary, in rheumatism, acute, 88

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

* indicates that only the title of a paper or article is given

Abbatt, J. D., 95
*Adams, F. H., 417
*Aikawa, J. K., 195
Ainger, L. E., 86, 88, 89, 208, 427
*Aird, I., 201
*Aldo, L. M., 200
Aldrich, R. A., 89
*Alejandro, Z. M., 200
Allende, M. F., 285
Allison, F., 111
Amira, A., 110, *200, 203, 209
Anderson, W., 194
*Andreini, A., 207
*Andres, G., 202
*Angrist, A. A., 417
Antoine, B., 113, 209
*Antonaci, B. L., 90, *106
*Ara, M., 207
Arbesman, C. E., 110
*Arce Gómez, E., 199
Arlet, J., 199, *427
Arneil, G. C., 426
Arnold, H. L., 287
Arnold, J. G., 96
Aronoff, A., 197
*Arturo Lozano, L. H. P., 199
*Asano, N., 424
Atkins, E., 111
*Attali, P., 294
*Aufdermaur, M., 98
*Aune, S., 200
*Ausenbachs, A., 98

Bach, C., 414
Bader, M. E., 85
Bader, R. A., 85
Baggenstoss, A. H., 101
Bailey, A. A., 422
*Baird, J. P., 200
Ballabio, C. B., *98, 110, 203, 209
Banowitch, M. M., 203
*Barbaso, E., 421
*Barbera, V., 423
Barceló, P., *106, 294, *421
Barkin, R. E., 281
Barr, J. H., 93
*Barrow, J. G., 195
Bartfeld, H., 283
*Basevi, A., 417
Batalla, E., 206
Batterman, R. C., 282
Bauer, W., 94, 97
Bauwens, P., 201
Beattie, J. W., 108
*Beck, J. C., 294
*Becker. R., 98
*Beiglböck, W., 427
*Beller, M. L., 200
*Berardinelli, W., 97
Bergamini, A., 110
Berman, L. B., 282
*Bertin, —, 202
*Best, M., 279
*Bickel, G., 427
Biörck, G., 84
*Bishop, C., 98
Black, R., 93
Blackburn, E. K., 286
*Blanco, E. M., 98
Blodgett, F. M., 424
Blumberg, B., 420
*Blumencron, W., 285
Boake, W. C., 206
Bobrovskaya, G. D., 428
Bocking, D., 94
*Böni, A., 419
*Boisver, P. L., 424
Boland, E. W., 278
Boldt, H. A., 111
Bollet, A. J., 93, 286, *294
Bonati, B., 110
Bonessa, C., 112
Bonfils, S., 113
Bonnet, P., 114
Bordier, P., 292
*Bosch Casañs, J., 288
Boselli, A., 112
*Bourel, M., 97
Bowie, M. A., 107
Brandao, N., 99
Braun, K., 275
Braunstein, H., 205
Breese, B. B., 87
Brill, A. B., 86
*Broch, F. M., 98
*Brocher, J. E. W., 98
Brøchner-Mortensen, K., 91
*Brockett, J. B., 424
Brodey, M., 290
*Brody, S., 423
Brown, B., 203
Brown, E. M., 107
Brown, W. M. C., 95
Brühl, W., 201
*Brummund, W., 427
*Brusch, C. A., 202
Bunim, J. J., 93, *200, 286
Burgin, L., 424
Burke, J. B., 194
Burrage, W. S., 112
*Bustamante, F. F., 201
*Buzard, J., 98
Bywaters, E. G. L., 197

Camara, A. A., 106
*Campo, C., 277
Cannon, P. R., 425
Cantarutti, F., 87
*Capponi, G., 106
*Carcassi, U., 417
*Carcassi, V., 207
*Carlson, F. S., 289
Carmichael, D. B., *90, *195
Carreras Bayes, A., 198
Cartesegna, F., 289, *294, 427 *bis*
*Caruso, A. C., 201
*Caselli, P., 106
Casolo, G., 84
Catanzaro, F. J., 275
*Cats, A., 279
*Cauwenberge, H., 102
Cecchi, E., 281
*Cernuschi, G., 195
*Cervini, C., 424
*Chait, B., 202
Chamovitz, R., 275
Champlin, B., 203
*Chaouat, Y., 98
*Chaptal, J., 277
Chasen, W. H., 102
*Chateau, R., 277
*Chevallier, J., 97
*Chiappara, P., 97
Christiansen, J. V., 423
Christie, B. G. B., 107
Chulkov, E. G., 207
Ciafaloni, D., 84
*Ciocci, A., 424
*Cipolloni, C., 195
Cirla, E., 209
Clark, C. J. M., 199
Clark, E. C., 422
Clark, E. J., 85
*Clark, G. M., 427
Clark, R. M., 194
*Clarke, C. N., 417
*Clarke, N. E., 417
Claussen, F., 113
Cler, R., 97
Cobb, S., *98, *203
Cohen, A., 278, 280
Cohen, E. B., 112
*Collins, E. J., 427
Colsky, J., 203
Conestabile, E., 96
Conley, C. L., 422
Cope, C. L., 109
*Copeman, W. S. C., 279
Coste, F., 92, *97, 113, 197, *200, 209, *421
*Coster, F., 106
*Coulon, R., 202
Cournand, A., 85
Coverdale, H., 284
Coyer, A. B., 201
*Crane, T., 277
*Creveld, S. van, 200
Crisp, E. J., 107
Crittenden, J., 279
*Cudkowicz, L., 279
Curtarelli, G., 90
*Curtis, R. H., 201
*Curzio, A., 114

Da Fonseca, A., 99
Dal-Cortivo, L., 293
D'Amico, G., 110
Daneo, V., 92, 93, *98, *106, *207, 289, *294, *424, 425, *427 *bis*
Danowski, T. S., 86
Da Pozzo, E., 293
Darby, P. W., 417
Daves, M. L., 99
Davis, E., 275
Debeyre, N., 92, 292
*Debray, M., 419
Debré, R., 426
*De Carlo, M., 279
Decourt, J., 293
*De Dalmases Gosé, R., 202
Delarue, J., 105
Delbarre, F., 92, 113
De Marchin, P., 283
*De Oliveira, P. P., 195
De Sèze, S., 92, 284, 292
*De Vecchis, B., 421
De Vita, P., 194
*Díaz Tellechea, C. M., 000
Diehl, A. M., 415
Dietz, H., 287
Di Nardo, A., 84
Disney, F. A., 87
*Dolcetta, B., 195
Done, A. K., 86, 88, 89, 208, *427
*Dordick, J. R., 91, *419
*Dorfler, F., 202
Doumic, J.-M., 293
Dourdou, G., 416
Dubois, E. L., 100, 422
*Dulong de Rosnay, C., 419
Dunsmore, R., 278
*Durupt, L., 98
*Dyrenfurth, I., 294
*Edström, G., 194
Efimova, G. M., 282
Egdahl, R. H., 292
Egemose, T., 94
*Eggink, A. A., 200
Ehrenreich, R. J., 110
*Einaudi, G., 423, *424
Eisenbeis, C. H., 93
Eisenstadt, W. S., 112
Elster, S. K., 277
Ely, R. S., 86, 88, 89, 208, *427
Emerson, P. A., 278
*Enzinger, J., 106
*Epstein, W., 289
*Erlendsson, F., 199
Escarpenter-Oriol, J., 198
Eyquem, A., *289, *424

*Fairbanks, R., 293
*Fannes, E., 277
*Farinella, A., 202
*Farneti, P., 421
*Fassbender, H. G., 90
*Fau, R., 277
*Fauré, C., 421
Fayolle, M. C., 274
*Fazio, B., 95
Fearnley, G. R., 197
Feldmahn, A., 206
*Ferond, M., 195
Ferraris, F., *95, *114
Ferrer, M. I., 85
*Fernández del Vallado, P., 427
*Fernández Mendy, J., 277
Feys, J., 282
Fife, R., 276
*Finck, P. A., 200
*Fink, R., 200
Fischer, F., 91, *113
*Fisher, M., 279
Flavell, G., 428
Fletcher, E., 288
*Fontan, A., 207
*Forbech, V., 280
*Forest, A., 97
*Forest, G. K. de, 424
Forestier, J., 283
*Forist, A. A., 427
*Forster, K. M., 421
*Fórster, O., 207
*Fortunato, A., 207
*Fournie, A., 282
Fowler, W., 285
Foz, A., *106, 206
*Franco, G., 114
*Frank, A., 106
*Fraschina, H. L., 277
Frazier, L. E., 425
Frick, P. G., 98, *285
Friedman, I. A., 102
Friedman, J., 285
Friedman, S., 273, 274
Fyfe, W. M., 90

*Gaglio, M., 106
Galli, T., 111, *420
*Galmiche, P., 195
Gamp, A., 103, *207
García López, G., 294
Garcin, R., 101, 287
*Garric, P., 208
*Gaulden, E. C., 202
*Gautier, J. C., 294
Gensler, W., 284

*Giacomasso, P. P., 200
Gibson, C. D., 194
Gil, J. R., 276
*Gilmore, H. R., 202
*Gilpin, W. A., 202
*Giomi, C., 97
*Giordana, M., 207
*Giroud, C., 294
*Giuliani, V., 202
Gjessing, H. G. A., 112
Gluck, E. J., 91
Godlewski, S., 101
Goldberg, B., 205
Goldberg, R. F., 290
*Goldin, C., 200, 281
Golding, J. R., 199
Goldner, M. Z., 285
*Golz, G., 427
*Gosling, J., 279
*Gospodinoff, A., 200
Gould, D. M., 99
*Grasse, L. A., 202
Gray, J. W., 93
Greenman, L., 86
Gribetz, D., 424
Griffin, J., 282
Grossman, A. J., 282
Groulade, J., 281
Gruner, J., 101, 287
*Guilleminot, R., 200
Gydell, K., 425

Habib, R., *102, 204
*Hagerman, G., 285
Hamilton, T. R., 415
Hamwi, G. J., 290
Hansen, K. B., 91
Hardouin, J. P., 113
Harris, R., 95, 420
Harris, S., *207, 274
Harris, T. N., *207, 273, 274
*Harris-Jones, J. N., 205
Harrison, R. J., 109
Hart, F. D., 199
Hartfall, S. J., 108
Harvey, R. M., 85
Haserick, J. R., 422
*Hasson, A., 419
*Haydu, G. G., 208
*Haynes, B., 279
Hecht, M. S., 416
Hell, F., 86
Hemphill, W., 87
*Henckel, H., 97
Henneman, P. H., 112
*Henry, C., 202
Hermann, I. F., 420
Hersh, A. H., 200
*Hertz, H., 90
Heymann, W., 107
*Hillman, R. W., 90
Hirschfeld, I., 89
Hirschowitz, B. I., 111
*Hoenig, L., 90
*Hoesch, K., 98
Hoffmann, R., 207
Hofstra, D., 416
Hollander, J. L., 107
*Holleman, E. J. W., 202
*Holonko, V., 421
Holopainen, T., *98, *200, *207, *279, 418, *419
Holsti, J. E., 94
*Houli, J., 419
Houser, H. B., 85
*Hubault, A., 200
*Hubbard, J. P., 90
*Huffman, E. R., 427
Hughes, R. H., 425
Hume, D. M., 292
*Hunziker, H., 106

Ibarra, J. J., 276
Iezzoni, D., 424
Irwin, J. W., 112
Isorni, P., 416
Izak, G., 426

Jacobs, J. H., 94, 288
*Jacobson, H. G., 200
Jacox, R. F., 206, 414
Jacqueline, F., 281, *289, *424
*Jahn, H. J., 201
*Jarrett, S. F., 280
*Jean, R., 277
Jessar, R. A., 107
Jeune, M., 274
*Jochem, E., 424
*Johnson, A., 289
Johnston, J. A., 416
Jordal, R., 417

Kalliomaki, L., 277, *289
Kanof, A., 103
*Kasanen, A., 106
Kaufmann, H., 416
Kelley, V. C., 86, 88, 89, 208, *427
Kelly, M., 201, 418
Kendall, P. H., 107, 291
King, J. H., 112
*King, S. H., 95
*Kleinschmidt, T., 419
Knight, G. H., 285
Knowelden, J., 288
Koch, F., 425
Koets, P., 203
Kogan, B. B., 000
*Kolde, H., 202
*Kooptzoff, O., 417
Kornel, L., 275
Koskinen, H. M., *200, *207, *279, 418
Koupernik, C., 209
Krewer, B., 196, *294
Kron, K. M., 420
Kruger, C., 207
Kubistova, V., 293
*Küster, F., 194
Kuhns, J. G., 280
Kuhns, W. J., 279
*Kuipers, F., 200
*Kuipers, R. K. W., 200
Kulka, J. P., 94
*Kulonen, E., 208
*Kurtz, C. M., 90
Kuttner, A. G., 193
Kuzell, W. C., 203, 204
Kuzma, J. F., 414

Lacapère, J., 92
LaDue, J. S., 193
Laine, V., *98, 196, *200, *207, 418, *419
*Lalliomäki, L., 106
Lambert, P., 101
Lambling, A., 113
*Lamphier, T. A., 000
Landau, J., 275
Lansbury, J., 419
*Lanty, R., 419
Lanza, I., 416, *417
Lapresle, J., 101
Lasky, M. A., 279
*Lasselin, —, 202
Laurent, F., *97, *200
Lawrence, J. S., 421
*Layani, F., 98
*Leal, J. P., 427
Lee, P. R., 198
Leeper, R. W., 285
Lemon, H. M., 102
Leveque, B., 426
Lévy, M., 98
Lewis, A. J., 415
Lièvre, J. A., 288, *294
Liljestrand, A., 105
Lindemann, L. C., 194
Lipsett, M. B., 425
*Litter, M., 202
*Lodeon, J., 207
Lombard, G., 287
London, P. S., 196
Looney, J. M., 102
*Lopez, E., 95
*López Toga, A., 294
Lorch, P., 196, *294
Losner, S., 103, 105
*Lövgren, O., 421
Lowman, E. W., 95, 198, 278
Lubschez, R., 88
*Luca, S., 106
*Lucchesi, M., 417
*Lucchesi, O., 417
Lucherini, T., 96, *202, 281
*Luetscher, J. A., 201
*Lukash, L., 417
Lustok, M. J., 414
*Lutembacher, R., 417
Lutz, W. B., 100
Lyard, —, 209
Lynch, J. B., 423
Lyon, D., 416

*McClendon, R., 279
McCue, C. M., 194
McEwen, C., *200, *293
McIntosh, D., 289
*McKusick, V. A., 285
McSwiney, R. R., 293
Maggi, C. A., 84
*Mai, H., 90
Makarenko, I. I., 279
Mäkinen, G. L., 418
Mäkinen, P., 418, *419
*Malaguzzi-Valeri, C., 423
Man, H. X., 287
Mankle, E. A., 203
*Manuel, J., 417
*Marañón, G., 421
Marche, J., 96, *200, *281, *282
Margolis, H. M., 93
Marie, J., 197
*Marino, T., 200
Markham, R. L., 288
Markowitz, M., 87, 193
Marmont, A., 100
Marquézy, R. A., 414
Marrazzi, G., 92, *93, 424, 425, *427
Mars, G., 112
Marson, F. G. W., 203
Martel, S., 422
Marten, R. H., 286
Martino, N. B., 426
Martz, E. W., 93
Mason, A. S., 293
Massell, B. F., 273, 276
Massias, P., 92
*Masturzo, A., 202
Mata Lopez, P., 284
Mateer, F. M., 86
Matteo, J. di, 414
Matthews, L. W., 107
*Mauer, E. F., 201
May, J. S., 415
*Mayeda, A., 424
*Mayne, G. O., 202
*Mazzone, O., 106
Medical Research Council/Nuffield Foundation Joint Committee on Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases, 195
Merchant, W. R., *98, *203
Merrick, E. Z., 93
*Mesnier, F., 207
*Meyer, G., 201
Meyer, M. P., 97
*Miccoli, G., 421
*Michael, M., 113
Michard, J.-P., 293
*Michel, J., 294
Michotte, L., 91
Middlemiss, J. H., 280
Mignot, J., 105
Millard, J. B., 95, 420
Miller, A. T., 108, 109
Miller, J. M., 276
*Miller, P. B., 95
*Miller, S. T., 200
Mills, I. H., 293
Minor, Z., 426
Mirouze, J., 85
*Mitolo, G. R., 195
*Moffatt, J. L., 114
Mole, 199, *427
*Monateri, P. C., 98
Morbidelli, R., 416, *417
Moreau, R., 97
Morel, L., 277
*Moreno Blanco, E., 288
Morgano, G., *95, *279
Moore, J. E., 100
Morpurgo, M., 112
Morris, A. J., 275
*Mosher, R. E., 417
*Motta, L., 195
Mozziconacci, P., 209, *417
Muir, H., 206
Murdoch, W. R., 276
Murnaghan, G. F., 289
Mylius, K., *114, 285

Nabarro, J. D. N., 107, 291
*Najib-Farah, —, 288
*Nalagan, D., 421
Natale, P., 96, *97, *202
Naugler, W. E., 203, 204
Needleman, H. L., 273, 274
Neill, J., 292
Nelson, C. T., 290
Nelson, D. H., 292
*Nerb, L., 90
Neustadt, D. H., *279, 283
Nevé, R. A., 89
Nielsen, J. P., 423
*Noferi, G., 202
Nolke, A., 416
Norymberski, J. K., 290
Nydick, I., 193

*Ogburn, C. A., 207
*Olash, F. A., 279
Olhagen, B., 105
Olsen, A. M., 101
*Onate, J., 199
Opie, L. H., 286
Orcese, L., 84
*Orihara, M., 424
*Ortiz de Montellano, E., 199
Ostriker, M., 279
Ostriker, P. J., 279

*Paci, A., 195
*Pätzold, E., 200
Pagel, W., 101
Pani, K. C., 205
*Papas, P. N., 202
Papotti, G., 416
Parhami, Y., 419
Pasargiklian, E., 110
*Pasquier, P. du, 419
Patet, J., 277
Patterson, M. B., 293
Payen, J., 105
Payot, J., 416
*Peacock, P. B., 195
Peak, W. P., 420
*Pearsé, A. G. E., 279
Pearson, O. H., 425
*Pérez de Salazar, J., 199
Perol, R., 97
Perosa, L., 194
Pfeiffer, E. F., 90
*Piguet, B., 419
*Piñol, J., 202
*Pizon, P., 285
Platt, W. D., 94
Plotho, B. von, 207
*Poker, N., 200
Pollard, H. M., 111
*Polosa, P., 195
Pond, M. H., 109
*Ponsonnet, G., 98
*Ponte, E. del, 200
*Poppel, M. H., 200
*Porcelli, M., 417
Potter, T. A., 281
*Preston, R. L., 199
Prunieras, M., 423
Prunty, F. T. G., 293
Purnell, D. C., 101
*Putois, J., 208

Radnóti-Recht, I., 86
Ragan, C., *289, 420
Rammelkamp, C. H., 275
*Ramos, J. M., 199
Rampon, S., 113, 209
Rancati, G. B., 110
Rantz, L. A., 205
Rascol, A., 199
*Ratti, G., 200
*Ravault, P., 98

*Ravazzoni, C., 95
Reboredo, A., 294
Rejholec, V., 102
Retboll, G., 94
*Rhyne, M. B., 195
*Riccardino, N., 106
*Rich, H., 90
Richards, D. W., 85
Richir, C., 113
Riley, V., 424
Rintelen, F., 421, *421
*Rivano, R., 106
*Rizzi, M., 95
Roantree, R. J., 205
Robecchi, A., 92, 93, *106, *203, 289, *294, 425, *427 *bis*
Robin, J., 92
Rodriguez, H., 276
Rohr, K., 427
Römcke, O., 418
Ropes, M. W., 94
Rose, F. C., 94
Rose, I., 280
*Rosenbaum, J., 203
Roskam, J., *102, *421
*Rossi, R., 207
*Rother, K., 106
*Rothschild, H. B., 427
Roussel, A., 105
Roy, S. B., 273
Royer, P., 426
Rubens-Duval, A., 92
*Ruelle, M., 199
*Ruffie, R., 208, *282
*Ruggieri, P. A., 208
*Ruiter, M., 202
Ruiz Moreno, A., *114, *199, *294, *421
Rusk, H. A., 198
Rusoff, J. H., 89
*Russ, J. D., 427

Sairanen, E., 418
Sala, G., 110, 203, 209
Salt, H. B., 289
Saltzman, H. A., 273
*Salvatella Viñals, J., 285
Samet, P., 85
*Sannazzari, G. L., 417
Sans Solá, L., *202, *294, *421
*Santamaria, A., 294
Sariols Gomez, M., 198
*Saslaw, M. S., 195
Sayre, G. P., 422
Scalabrino, R., 90
*Scardigli, G., 95
Schaffarzick, R. W., 203, 204
*Schaffner, F., 277
Schemm, F. R., 106
*Scherbel, A. L., 277
Schergna, E., 87
Schiavetti, L., *95, *97, *114
*Schimanski, J., 106
Schindler, H., 103
Schmid, J., *200, *207
Schöffling, K., 90
Schreiner, G. E., 282
Schrub, J., 414
Schultz, I., 415
*Schumacher, H., 106
Schwartz, S. O., 102
*Scialabba, D., 293
Scott, G. E., 280
*Scripilliti, S., 97
Sebardt, G., 196
*Secondo, G., 424
Sée, G., 197
Seely, J. R., 88, 89, 208
*Segagni, E., 195
Segal, S., 286
*Selinkoff, J. J., 200
Serre, H., 85
Shapiro, D. J., 107
Shelden, W. E., 416
Shephard, R. J., 413
Sherrard, W. J. W., 288
*Shichikawa, K., 424
Sichère, R. M., 98
*Silberberg, M., 280
*Silberberg, R., 280
Skanse, B., 425
Skillman, R. K., 102
*Skogrand, A., 419
Sladden, R. J., 421
Slonimskaya, V. M., 428
Smirnov, N. P., 208
Smith, J. F., 99
Smith, M. R., 111
Smith, R. T., 420
Smukler, N. M., 107
*Smyth, C. J., 427
*Södring, R., 98
Solari, S., *106, 111, *420
Solem, J. H., 418
Spector, S., 107
*Spies, T. D., 294
*Spira, C., 201
Spurrier, W., 102
Stecher, R. M., *98, *200, *202
*Steel, S. J., 114
Stefanini, M., 426
Steffen, C., 103
*Stein, I., 200
Stein, Y., 426
Steinberg, I. H., 94
Stemmermann, W., 97
Stewart, J. S., 291
Stillman, J. S., 281
Steinbrocker, O., 283
Stollerman, G. H., 89, 192, 413, 415
Stolzer, B. L., 85, 93
*Stone, R. E., 294
*Storck, H., 285
Streeten, D. H. P., 111
Strickland, B., 102
Stubbs, R. D., 290
Sturgis, G. P., 273
Suárez, R. M., 294
Sura, V. V., 279
*Sutton, G. C., 277
Suzman, M. M., 205
Swift, S., 204
*Szalóczy, K., 114
*Szersnovicz, G., 207
*Szucs, M. M., 421

Talbot, N. B., 424
*Talbott, J. H., 98
*Tamatani, Y., 424
Tang, J., 193
Taranta, A., 413, 415
Tedeschi, G. F., 110, 105, *277
Thierry-Mieg, J., 284
Thiers, H., 114, 277
*Thompson, D. J., 000
Thulin, K. E., 104
*Timpe, A., 113
Toloknova, E. A., 276
*Torino, A., 202
*Toso, M., 417
Toussaint, J., 199
Treip, C. S., 101
*Trías de Bes y Terrés, J., 207
*Trueta, J., 280
Turner, R., 278, 280
Tuzi, T., *106, *202
Tweedy, P. S., 413

Udell, L., 107
Umberger, C. J., 293
*Usseglio, G., 200

Vainio, K., *98, 196
*Vaisman, S., 195
Valentin, B., 294
Valles, W. C., 424
*Van Bogaert, A., 277
*Vaughan, J. H., 424
*Venanzi, S., 97
Venner, A., 413
*Venning, E. H., 294
*Verger, P., 207
*Verspyck, R., 200
Vicnon, G., 277
*Vignon, G., 98
*Vilanova, X., 202
*Villela, Nunes, C., 202
*Visioli, O., 417
*Vliers, M., 102
*Vogel, R. A., 113
*Voit, K., 202
Volk, B. W., 103, 105
*Volpicelli, M., 106

*Waghemacker, —, 202
Wagner, B. M., 205, *277
Wagner, V., 102
Walker, G., 291
*Wallace, H. M., 90
Wallace, S., 203
*Wallach, J. B., 417
*Waller, M. V., 424
*Walsh, R. J., 417
Wang, D. M. K., 112
Warren, J. E., *98, *203
*Wasastjerna, C., 106
*Wasserman, C. F., 427
Watt, J., 423
Weerekoon, L. M., *200, 281
*Wegelius, O., 106
Weigand, F. A., 86
Weimer, J. R., 112
Weinberger, H. J., 97
*Weinstein, A. B., 90
Weismann-Netter, R., 196, *294
Weiss, R. S., 204
*Weissenbach, R., 200
West, E., 416
*Westergren, A., 98
*Wilkinson, L. H., 420
*Williams, D. W., 202
*Wilson, G. M., 427
*Wilson, H., 293
*Wirtschafter, Z. T., 202
Wood, H. F., 277
Wood, W. B., 111
Wróblewski, F., 193
Wulff, H. B., 425

*Yasuda, J., 424

*Zalaffi, R., 90
Zanazzi, A., 84
Zarrabi, M., 419
*Zeldis, A., 95
*Ziff, M., 293
Zinkham, W. H., 422
Zion, M. M., 205
*Zondek, S. G., 95

277

03
7
00, 281

196, *294

02